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THE THREE PILLARS OF CLINICAL RESEARCH*

BY

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Despite its title, this paper is really addressed to surgeons. The message, if there be a message, may be applicable to other groups within the profession, but I am not qualified to expound on the difficulties met with or the foibles displayed by my medical, gynaecological, paediatric, geriatric, or other colleagues in the course of their clinical inquiries; and so it is to the surgical fraternity primarily that I address myself.

As surgeons, we handle a great deal of material which is properly the substance of clinical research, but I am afraid that in many instances we handle it clumsily so that the final product is uncertain and open to criticism. Moreover, we are unduly addicted to armchair theorizing, and are, for instance, in the habit of extolling a method of therapy which is little more than the creature of our contemplation and has never been subjected to the rigours of experimental trial. Why we should behave like this when the man who said, "Why think? Why not try the experiment?" was himself a surgeon, it is difficult to say. Surgeons started off as anatomists, then they became pathologists, so that thirty years ago it was still possible to quote the aphorism: "Know your anatomy, know your pathology (and you'll) know your surgery." To-day, surgeons are physiologists; to-morrow perhaps they will be scientists, and so, more than two hundred years later, arrive breathless at the summit reached with such easy mastery by John Hunter.

Imagine a surgeon dissatisfied with his present methods of treatment and conscientiously and hopefully thinking how he might improve them. He summons his anatomical, pathological, and physiological knowledge to his aid. "Placed there," he will say, "it will have a better blood supply." "Thus and thus the lymphatics will be more completely removed." "Done so, the acid will be less injurious; radiotherapy, if necessary, more efficacious; the anastomosis more secure; the respiratory excursions less impeded; the enzymes more fruitful"; and so a new operation is born. So far, so good, but in ten years there is found to be a snag and students ask plaintively, "What is this operation 'gastrorrhaphy,' mentioned so enthusiastically in my father's textbook?"

The Stochastic System

The pattern for research should be, first, the idea; second, and if suitable, its trial on the experimental animal; thirdly, its trial on human beings; and fourthly, its announcement in the surgical journals. In much surgical research the two middle steps are omitted. One of the reasons for this is that surgeons are unfamiliar with the idea, which is a commonplace for physicists, of the stochastic system. An example will serve to show what is meant.

If I am completely uncertain which of two courses to adopt, I might toss a coin and act according to the dictates of what befell. I should regard this then as entirely a matter of chance, but if I knew all the facts this would not be the case. If I knew, for instance, the exact weight of the coin, its size, the strength of the impetus imparted to it, and the site of impaction in relation to its centre of gravity, the temperature and humidity of the atmosphere, the distribution of densities in the coin in relation to its centre of gravity, the distance it had to fall, and perhaps other factors such as the stickiness and temperature of my fingers, I should be able to calculate whether the coin would come down heads or tails. If, that is, I knew what are called the "hidden parameters," tossing a coin would no longer be a matter of chance. The spinning coin is not transgressing the principles of causality, and whether it comes down heads or tails is governed by strict law.

We may contrast such a system with that obtaining inside an unstable atom such as an atom of radium. Sooner or later this atom is going to discharge an emanation and become degraded to radon. On analogy with the above example we might argue that if we knew all the processes going on within the nucleus we could predict exactly when the atom of radium would disintegrate and that it is only the complexity and minuteness of these hidden parameters which prevents us from doing so. This, however, is not the case; no amount of knowledge, however intimate, of what is going on inside the nucleus would help us to determine whether the radium atom would disintegrate in the next ten seconds or in the next ten years. Such systems where the reactions are not individually determined according to the principles of causality are called stochastic systems.

Now, the human body has so many hidden parameters that to work out from the armchair how it is going to behave after a certain operation is a most uncertain enterprise. These hidden parameters are so multifarious that we may for practical purposes regard the human body as a stochastic system; indeed, if we admit the principle of free will, and if I understand him aright *pace* Spinoza's "metaphysical determinism," it *is* a stochastic system.

Trying Out

It is therefore the number of hidden parameters or even the possible stochastic nature of the system with which we are dealing which makes the application of cybernetic principles to the human organism so chancy.

*A lecture to the Medical Faculty delivered at Queen's College, Dundee, on October 30, 1958.

The trouble with advocating a course of action which in practice turns out, perhaps only in the long run, to be without value is that all the work has to be undone and a start made afresh with the consequent wasting of years of effort and the obstruction of real advance in the meanwhile. Let us take it as an axiom then that, however sound the idea might seem to be and however carefully checked in all its apparent ramifications, before it is publicly advocated it must be tried out so as to "see," as they say, "what happens in practice."

Now, the business of "trying out" is the very "bricks and mortar" of the edifice of clinical research, and while more and more flags are being put out from the upper stories of this building I would wish here to explore a few of the foundations, the very pillars upon which the structure of clinical research reposes. The tour which I would ask you to take with me in a very humble and elementary way is not unlike that taken on a grand scale by Bertrand Russell (1919) in respect of the far more complicated subject of mathematics. It was the self-appointed task of Russell and of his collaborator, Whitehead, to delve down rather than to soar on upwards, and by exploring the foundations of mathematics to lay bare its fundamental structure and so strengthen and accelerate the whole of mathematical thinking. It might be helpful if we tried to perform in miniature the same sort of analysis for clinical research.

It would seem to me that the structure of sound clinical research reposes on three pillars—control, mensuration, and analysis—and it is the purpose of this paper to examine these pillars in detail.

CONTROL

It might be regarded as an impertinence to include a description of this "pillar" in a paper addressed to postgraduates, but sad experience in the past fifty years shows that this is unfortunately not the case. Advances in at least two of the major branches of surgery have been bedevilled by the results of widely advertised research improperly controlled. The swings to and away from some much-canvassed methods of therapy, almost it would seem at the dictates of fashion, are, to say the least of it, inelegant in a so-called learned profession, and are really quite inexcusable departures from the demands of a scientific discipline.

Now, there are controls and controls, and it may not be practicable for the investigator dealing with human material to establish the rigid controls possible in the laboratory. Nevertheless, he should arrange for the most accurate method of control available. One common practice that cannot be too sternly condemned is to arrange and carry out a piece of clinical investigation and then when it is completed to look round in the literature or in the past records of the hospital for something with which to compare it. Such so-called "control" is from the scientific point of view worthless, as the two groups so contrasted are not comparable. For instance, to attempt to compare a group of cases treated for ulcerative colitis in 1957 with a group treated in 1937 takes no account of the innumerable advances, perhaps only in the management of incidentals, that have taken place, and which in sum may make all the difference between success and failure. In such a hypothetical instance one could cite improved antibiotics, better *x*-ray diagnosis, an appreciation of the Rh factor, a more complete understanding of electrolyte and fluid balance, change in the nutritional and environmental circumstances of the population, and so on almost *ad infinitum*. When stated in this way, it would seem almost ludicrous that anyone should dare in a scientific paper to make such comparisons and call them controls, and yet this is being done continually.

Another objectionable practice is to compare a series of cases treated in one locality with a series treated in another. Even if these are contemporaneous, the circumstances are so different, the skills and disciplines involved in making the diagnosis and in applying the routine methods of therapy are so variable, that, without taking into account the well-known habit of disease to behave differently under different climatic and geographical conditions, it should be abundantly clear that a comparison of two such groups has practically no scientific value.

It might be objected that humane considerations demand that a measure which appears promising should be tried out on any patient without having as a control a group which is denied the possible benefits which such a measure might confer. This is rarely a real difficulty in practice. If the measure is so effective that its prescription is vital, as in the instances of penicillin and insulin, then this effect is at once obvious. The group so treated display such a pronounced advantage over those that have just preceded them in the same institution and over those in other hospitals at the same time where the measure is as yet unavailable or unknown, that the most austere critic would never dream of denying to any of his patients the benefits which have been so clearly established.

Where, however, the choice is between one antibiotic and another, between one insulin preparation and another, or over the use of some drug or new operation which "looks as though it might be an improvement on all that has gone before," then it is far better that these measures should be tested scientifically with adequate control, so that ideas which have to be abandoned a few years later are not foisted on the profession, with all the frustration, suffering, and unnecessary expense which this entails.

In many instances, in determining the value of a highly promising method of treatment in an otherwise desperate or lethal disease the embarrassment of having a group of cases as a control may be avoided by using the patients as their own control. Thus, after a preliminary period of stabilization during which the essential investigations are undertaken, the remedy in question is applied and the pre- and post-treatment courses can properly be compared in a number of individuals (Fig. 1).

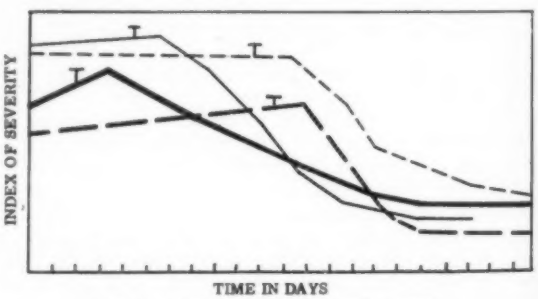

FIG. 1.—The patient as his own control.

What in fact is being urged is not the insistence on a rigidity of control only possible in all circumstances in laboratory work, nor that any patient's life should be jeopardized in the interests of science, nor that patients should be incommoded to any greater extent than is inseparable, for instance, from the needs of teaching, nor that any doctor should compromise with his conscience; but simply that he should bear in mind the necessity for controls if any real advance is to be made in medicine and that he should apply these with common sense whenever they are applicable.

Very few of the thousands of advances that are made each decade in medicine or surgery are of world-shaking import in the way that the discovery of penicillin or insulin might be regarded. Many of them are only modest improvements on what has gone before, and many new ideas which promise so much turn out to be less effective

than established methods. Within this framework, then, which comprises 99% of the field of clinical investigation, rigorous control causes no undue suffering, and is obligatory if we are to know the real value of the measure under discussion. As in navigation, so in clinical surgery, it is highly desirable to know where you started from, if possible, where you are going, and, within certain limits of error, where you are.

Randomization

If two groups are to be formed, one the experimental group and the other the control, then by far the best method of doing this is by randomization. It might be thought that to allot cases to each group alternately might be as good a way as any, but there are certain objections to this method. For instance, the whole series comprising both trial and control groups probably belongs to a certain class of case so that the investigator may have to decide whether any particular case conforms to the class or whether it should be discarded. This in itself may require considerable judgment, as for instance in deciding whether a case of hypertension would be suitable for surgery. If the method of dividing the series into the two groups were by taking alternate cases, then the investigator, if biased, and bias must always be assumed, might be tempted to exclude from the investigation altogether an unfavourable case if he was aware that the next in the series would automatically be placed in the category in favour of which he had a conscious or unconscious bias. Randomization should be undertaken only when the investigator himself, or another person, has decided that the case falls into the class. A card may then be drawn from a box originally containing a specified number of pairs of cards marked "treat" or "control" and the patient is allotted to the "treat" or "control" group, according to the instructions on the card.

Modifications of this method may be devised in order to exclude bias more completely. These methods include the "blind" investigations where the investigator is unaware of which method of treatment he is administering (a device clearly not applicable when comparing the effects of operation with conservative treatment), or he does not know when assessing the patient subsequently from which group he came. These elaborations must, nevertheless, be based on sound methods of randomization in the first instance. With all these precautions, however, loopholes through which bias may intrude still occur, particularly in small series. Thus if a group of six patients were being compared with a control group of six patients, and if, owing to the vagaries of chance, a run of identical cards were drawn early in the investigation, the increased chances of the opposite category being drawn towards the end of the series would probably be known to the investigator. This difficulty can be overcome in theory by keeping the investigator who decides whether the case is suitable in the first instance unaware of the way in which the draw has gone so far; but this is almost impossible in practice, particularly as this person may well be the one best qualified to carry out the subsequent treatment, and, in any event, it is an objection which hardly obtrudes in a big series until the very end, when it is unlikely materially to affect the issue.

A further refinement of this method of randomization may be introduced by arranging that sub-categories are paired together. Thus one box of paired cards may be made to apply only to those under the age of 40; another, to those aged 40 and over, or to any other selection of sub-categories which may lead to a more accurate pairing of like with like.

The Ethical Problem

At this stage we must inquire into the ethics of conducting an investigation involving the randomization of human patients. In the first instance, the rule is extremely simple, and is the fundamental one that if you would allow the choice of treatment to be made on a member of your own family or on yourself by the flip of a coin, then it is quite ethical to subject a group of patients to a randomized choice in this way. Certain outstanding problems in surgery fit quite comfortably into this category. Thus an investigation into the effect of lumbar sympathectomy on the incidence of gangrene in claudicants, the effect of surgery in a certain class of hypertension, or the relative merits of gastrectomy and gastrojejunostomy in certain types of duodenal ulcer could well be investigated by randomization without disturbance to the conscience.

This matter of conscience, however, can really be overdone. For instance, in trying to organize an investigation into the relative merits of radical mastectomy and the "Edinburgh method" of treatment of early cases of cancer of the breast, it was found that the advocates of radical mastectomy could not be persuaded to subject a control group to the Edinburgh method, because their consciences would not permit them to allow their patients to be subjected to such an inferior measure; the advocates of the Edinburgh school felt the same about radical mastectomy. Nevertheless, it should be possible to find a group of people who are in genuine doubt about this problem and who could therefore properly undertake an investigation of this kind.

The ethical problem becomes more acute as the investigation proceeds and it appears that one method of treatment is showing a clear advantage over the other. The rule here is just as definite, but is not at once so manifest as when the investigation is first promulgated, and the rule is that if it was ethical to start the investigation in the first place it would be unethical to desist until a clear-cut answer has been obtained. This might conflict with considerations depending upon what one would wish for one's own family or oneself, but this should not be so. If a significant result has been obtained, then the investigation is concluded and the difficulty does not arise. If it is simply an impression that one method of treatment is better than the other, then the feeling that you would hope that a member of your own family would, if subjected to the test, draw one card rather than another is little more than a gambler's hunch. To break up the investigation before a statistically valid result has been obtained would be to sacrifice all the value of the investigation hitherto and would be quite irresponsible. If the investigation was a proper one in the first place, it should be continued until at least a 5% level of probability has been achieved, or it has been decided that the two methods of treatment are so nearly comparable that no purpose would be served by prolonging the investigation, in which case the ethical problem does not arise.

For a discussion of the problem of when to put a stop to an indeterminate investigation the reader is referred to Finney's (1955) book, where this matter is fully analysed.

MENSURATION

Science depends upon measurement, and qualities that can be measured numerically are more readily comparable than those which cannot. If the marking is accurate and you get six marks in your examination and I get five, then you have done better than I. Even if the marking is not quite accurate, the school which averages six marks in the examination has done better than the school which averages five, and the larger the number of candidates the more accurately does this average reflect the difference between the two schools. If, therefore, we are comparing two methods of treatment it is most helpful if the results of the treatments can be compared numerically, by marks if you will. This method of expressing the results has the advantage that it is definite, and, moreover, it generally gives an idea of the degree of difference between two treatments. For instance, if the results of treatment can be expressed in terms of the death rate per thousand or the period of survival, then if, on the average, patients under treatment A survive five months and patients under treatment B survive eight months, and provided sufficient numbers have been taken, it is quite clear that treatment B

is to be preferred to treatment A. Furthermore, the figures give some indication of how much better the one treatment is than the other. There are, however, other equally important advantages of expressing results numerically.

Supposing the relation of treatment to a variable is being considered, then if the results of treatment can be expressed numerically a "scattergram" can be constructed and the relation, if any, established on inspection or by calculation. Fig. 2 shows a hypothetical investigation to determine whether the success of a certain treatment is dependent on the initial weight of the patient. The results of treatment are expressed as time in days before the temperature settles, and the scattergram shows, in a way more clearly than any amount of verbal description would have done, that there is such a relation and that fat people respond better to treatment than thin. For more accurate work an exact coefficient of correlation could have been calculated. Finally, where a numerical assessment of treatment can be

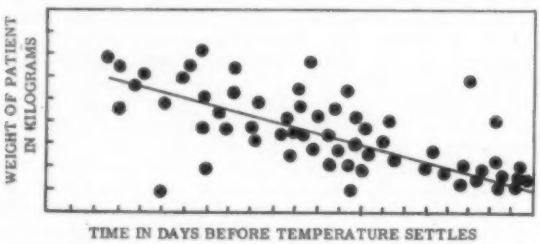

FIG. 2.—Scattergram relating weight of patient to the period of pyrexia.

provided the whole investigation is susceptible to statistical analysis, and extravagant claims which are really quite unwarrantable are not put forward.

When there are all these advantages of precise mensuration it is a pity that surgeons as a whole dislike figures and that this dislike is often so ingrained that they do the most illogical things with them if they have to use them at all, as, for instance, in marking examinations. In nearly all surgical examinations there is a desire to give more weight to one part of the examination than to others. It is usually "the clinical" which is singled out for this special attention. In the Treasurer's Gold Medal in Clinical Surgery at Guy's Hospital, for instance, it has been the practice from time immemorial to mark the papers out of 200 and the clinical out of 300. This of course has no effect at all, because as often as not candidate A, who is slightly better than candidate B in the paper, will get 155 marks to B's 150, and, being slightly worse in the clinical, will get 250 to B's 255, so that their total marks are the same and nothing has been achieved. What is clearly needed in order to add weight to one part of an examination is to increase the range of marking in this part of the examination and never mind about the maximum. The fact that this anomaly is by no means confined to Guy's Hospital, but invades Queen Square, whether it be under the aegis of the Royal Colleges or London University, and is in evidence in the examinations of many provincial universities as well, only serves to show how inexpertly medical men can behave when dealing with figures.

Another type of illogical error is exemplified in *Against the Law* by Peter Wildeblood (1957). There occurs there the following statement, with the so-called evidence which is intended to support it.

"It is, of course, perfectly obvious that only a very small proportion of this 650,000 is noticeably odd. It is equally evident that homosexuality is not, as some propagandists would have us believe, a kind of fashionable vice restricted to decadent intellectuals and degenerate clergymen. This idea is extremely useful to those who wish to influence public opinion against homosexuality, and it succeeds because the British people, on the whole, despise intellectuals and distrust the clergy. But it does not happen to be correct. In a recent survey of 321 court cases involving homosexuality, it was found that the accused men fell into the categories shown in Table I."

TABLE I.—*Categories of Homosexuals (Peter Wildeblood,* 1957)

Shop and clerical workers	16%	Schoolmasters	4%
Artisans (factory workers)	15%	Agricultural workers ..	4%
Transport and Post Office	11%	Clergymen	2%
Unskilled labourers ..	10%	Mentally deficient ..	2%
Armed Forces	10%	Independent means ..	2%
Hotel and domestic servants	7%	Unclassified	11%
Students, trainees, schoolboys	6%		

This table, of course, means nothing unless we are at the same time given the percentages of "shop and clerical workers," "artisans," and so forth in the general population. Indeed, it is not inconsistent with the possibility that all members of the above categories are homosexuals.

Incommensurable Qualities

This inability to think clearly in figures is often rationalized by claiming that so many of the results of clinical experiment cannot be satisfactorily expressed numerically. Some qualities of human behaviour are, of course, quite impossible to measure—such qualities, for instance, as bravery or fastidiousness; but this does not mean that inquiry related to these qualities *cannot* be given a numerical expression. For instance, if the 1st Battalion of the East Loamshires won 3 Victoria Crosses and 2 Military Crosses in the last war, whereas the 2nd Battalion won no medals and had a sergeant and four other ranks shot for cowardice in face of the enemy, there is good reason on purely numerical grounds for presuming that the 1st Battalion had a better morale than the 2nd Battalion, although morale is essentially a quality which cannot be measured.

Clearly a passion for mensuration can be overdone, as the following charming quotation from R. E. Dickinson (1958) attests: "Lord Kelvin said that we can know nothing of a matter unless we can measure it. Psychologists braced with their success in giving numerical values to I.Q. are now hoping to measure feminine beauty in precise units. The unit proposed is the milli-helen, the quantity of beauty required to launch exactly one ship."

Such endeavours to express essentially incommensurable qualities by numbers must of course be undertaken with great care. Often, however, if it is reasonable to adopt it, this method shows up in a vivid manner differences and relations which might otherwise be obscured in a mass of verbiage. A particularly valuable method of mensuration devised originally by Walpole and Paterson (1949) is the mean clinical value. This method of giving a numerical value to the effects of treatment is applicable especially to those conditions, such as advanced cancer of the breast, where there are apt to be many manifestations and where these manifestations may respond in a different manner to treatment or respond at a different time.

The working of the system is very simple, and depends upon deciding whether, as a result of treatment, a lesion is better than it was before treatment began or worse than it was before treatment began, or whether the situation is doubtful.

Mean Clinical Value

Before treatment all lesions are accurately assessed—by measurement if they are palpable or visible, and by studying their dimensions or densities if they are radiological. Subjective symptoms are better ignored, but the "presence" or "absence" of pain may well be a valuable index of the effect of treatment. In this way a baseline is made and the treatment is started. The patient is seen at four-weekly intervals thereafter and each lesion is again assessed. If the lesion has improved it is given 2 marks, if worse 0 marks, and if stationary or doubtful, 1 mark. These marks are then added together and divided by the number of lesions to obtain an average. The average is multiplied by the factor 6 to bring the figure to a manageable number, which is the mean clinical value (M.C.V.). It will be seen that the maximum M.C.V. is 12, which implies that all the

lesions are improving. An M.C.V. of 0 means that all the lesions are worsening, and an M.C.V. of 6 that the condition is stationary. This last mark may be due to the fact that all the lesions are stationary, or that half are improving while the other half are regressing, and it indicates, therefore, the response of the patient as a whole. The M.C.V. may have any figure between 0 and 12, and a graph can be drawn of the progress of a patient under treatment. The state of the lesions is compared with their state before treatment began and not with their state at the previous visit, because it is more satisfactory to have one standard than to have an ever-changing standard which is apt to lead to swings on the graph that have no real meaning.

The effect of this, however, is that, when a patient who has for some time responded to treatment begins to deteriorate, this deterioration is not at once reflected in the M.C.V. because the lesions may still be better than they were before treatment began and often there is a somewhat precipitate drop in the graph before death. This is, in practice, only a very slight disadvantage, because, certainly in the case of cancer of the breast, when a patient begins to deteriorate she does so very quickly, and the delay in the drop in the graph from this cause is generally only a matter of one period or at the most two periods. As has been indicated, if there is any uncertainty over whether a lesion is changing, then it is given a mark of 1. By the next visit this uncertainty has usually been resolved, and a lesion which looked as though it might have improved but about which there was some doubt has now unequivocally improved and can confidently be given a mark of 2. All that has occurred, therefore, as a result of the possibly mistaken assessment of the lesion at the visit when it was given the "uncertain" mark of 1 is that the shift in the graph has been delayed by four weeks. Conversely, the same applies to a lesion which seems to be deteriorating but about which there is some doubt, and the whole graph is therefore given a sure and steady delineation which properly represents the course of the patient under treatment, albeit with a slight latent period or what the cyberneticist might call "a threshold-controlled stability."

Radiological factors are assessed at every third visit in order not to multiply the number of *x*-ray films taken, and the previous mark allotted to this factor is retained in the interval to compute the M.C.V. for those two periods. This again leads to some lag, as the *x*-ray picture may have changed in the meantime and this is not reflected in the graph until later.

With all these slight and largely theoretical defects, the M.C.V. has proved in practice to be a tool of the greatest value in research. Thus, in comparing two methods of treatment, as for instance adrenalectomy and hypophysectomy, for carcinoma of the breast, the individual M.C.V. charts of all patients treated by one of these methods can be congealed into one average graph and compared with a similar average graph for the other method of treatment (Fig. 3).

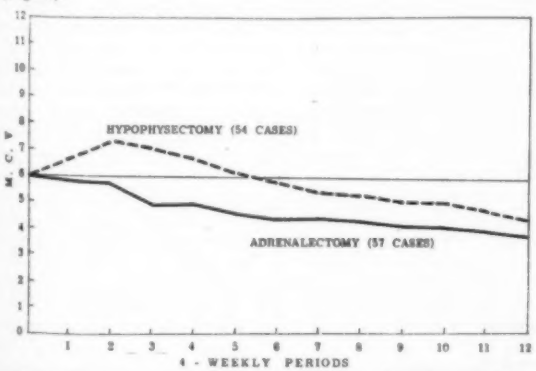

FIG. 3.—Response to adrenalectomy and hypophysectomy, taking the average M.C.V.s of all patients at four-weekly periods after treatment.

Again, by taking an average of all the M.C.V. records of a particular patient, a single figure can be made to represent the overall response of that patient to the treatment, and a table (Table II) can be made out which gives a good idea of the effect of this measure as a whole. By the use of

TABLE II.—*Effect of Oestrogen on 94 Cases of Advanced Cancer of Breast, as Expressed by Average M.C.V. Per Case—i.e., 17 Cases Had an Average M.C.V. Between 8 and 12, 39 Cases Between 7 and 4, etc.*

Average M.C.V. . .	12–8	7–4	3–0	Unable to take drug
No. of cases . .	17	39	31	7

the "average M.C.V." derived in this way it is also possible to construct scattergrams (Fig. 4) and so determine a relation or lack of relation between the success of treatment and such factors as age, mitotic-cell count, or what you will.

There is one flaw in the M.C.V. system so far practised that is a serious theoretical disadvantage, but which has been so unobtrusive in practice that its full implications have only recently been appreciated. If we consider a case, for instance, of cancer of the breast with multiple skeletal deposits and multiple skin lesions and in which there are so many lesions that it would be impossible to exploit them all, then it has been the practice to decide arbitrarily how many skeletal lesions and how many skin lesions should be taken as representatives to act as factors in assessing the M.C.V. Usually the obvious ones or the readily mensurable ones have been taken and the others have been ignored. If all the lesions vary in the same way with treatment, then it does not matter very much how many are taken as indices. If, on the other hand, one system improves while the other deteriorates, then it is clearly important how many factors have been taken in each system. For instance, to take an extreme and very unlikely case, if two factors have been taken in the skeletal system which is deteriorating and ten factors have been taken in the skin which is improving, the M.C.V. is 10; whereas if ten factors were taken in the skeletal system and two in the skin, the M.C.V. would be 2, which makes nonsense of the whole method.

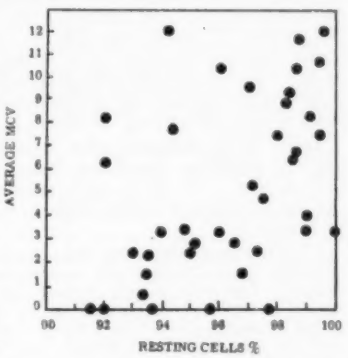

FIG. 4.—Scattergram relating M.C.V. to resting-cell count.

In order to repair the flaw in such unusual cases J. Hayward has suggested the following modification of the system which is now being put into operation. The lesions in each system are grouped and an average is taken of these; the mean of the grouped figures is then taken to compute the M.C.V. Thus, in the example cited above, the M.C.V. would be calculated from the fact that the skeletal system scored 0 and the cutaneous system 2, so that the M.C.V. would be $\frac{0+2}{2} \times 6 = 6$, however many or however few lesions were taken from either system. There is no method of computation which takes care of the case—one perhaps out of several hundred—where there are so many lesions in one system that a selection has to be made of representative factors, but where the lesions common to one system are behaving in a different way under treatment.

Stress has been laid on the defects of a system which in practice runs very smoothly. If a visitor to the breast clinic at Guy's Hospital, where this system has been used now for many years, is asked to give a mark—somewhere between

0 and 12—to the effects of treatment, and basing his opinion on a general clinical assessment, without recourse to exact measurement, it is surprising how closely his guess coincides with the computed value. To state that a patient has an M.C.V. of 9 is a quicker, more useful, and more vivid way of expressing the conclusion that this patient is responding in some degree to treatment and that it is worth while persisting with this treatment, but that not all the lesions are reacting favourably. Furthermore, the alternative is to fall back on the dangerous use of "clinical impressions" which has been productive of such fallacious conclusions in the past.

Recording Measured Data

If we now turn to another aspect of mensuration—namely, that of recording measured data—some consideration must be given to the punch-card system. Smyth and Bainbridge (1957a) have introduced an extremely useful system for tabulating punch-card records which enables the inter-relation of a number of factors to be studied readily. The article in which this method was described concerned the interplay of a number of obstetric factors such as the relation between stillbirths and post-maturity, forceps delivery and the duration of labour, and so forth. It included a specimen table consisting in fact of 32 variables, and was so alarming at first sight that it probably dissuaded many readers, who would otherwise have found the system extremely valuable, from pursuing the matter further.

Table III is extracted from their more elaborate table, and for simplicity shows the interrelation of only six of their factors. To quote, with certain modifications, from the paper by Smyth and Bainbridge, this table is constructed as follows:

"The principal cells on the *main diagonal* show the numerical incidence (upper figures) and percentages (lower figures) of 6 factors. The cells in the *bottom left-hand* half show the numerical incidence of patients having the two factors named in the intersecting row and column. (Where these factors are mutually exclusive, as in 'Breech' and 'Occipito-posterior,' the cell is left blank.) The cells in the *top right-hand* half contain two percentages—that is, the number of patients having both of the appropriate row and column factors expressed as a percentage of the total incidence of (1) the *column* factor (upper figures) and (2) the *row* factor (lower figures)."

"*To See if these Percentages Differ Significantly From the Means.*—Taking the lower percentage only, subtract it from the percentage in the principal cell on the same *row* (or vice versa); compare the answer with the figures in columns B to E on the same row; observe how many patients are needed for this difference to be significant; lastly, examine the principal cell in the same *column* to see if that number of patients occurs.

"Column A shows the minimum number of patients required in the *column* principal cell for the test to be applicable to that row."

Thus all the statistical analysis is worked out beforehand and all the clinical investigator has to do to see whether his results are significant is to use a table no more complicated, as the authors point out, than a mileage chart in the *A.A. Handbook*. For instance, by following these rules it will be found that manual removal will be associated with breech delivery in a highly significant fashion, whereas relative disproportion and toxaemia are not so associated.

The construction of columns A, B, C, D, and E is a simple statistical exercise which a friendly colleague with an elementary knowledge of these matters may undertake in a very short time by reference to the instructions contained in the original article and subsequent correction (Smyth and Bainbridge, 1957b). The figures given in columns B to E are simply twice the standard deviation.

To help in using this method, Garside (1958) has published a table for ascertaining whether differences between percentages are statistically significant, and the result can be picked out by little more than simple inspection.

Another technique for presenting results, which may be very valuable where three variables are involved, and which is much neglected by workers in clinical fields, is the three-dimensional graph. A good example of this taken from a paper by Skoog (1957) is shown in Fig. 5, where the effect

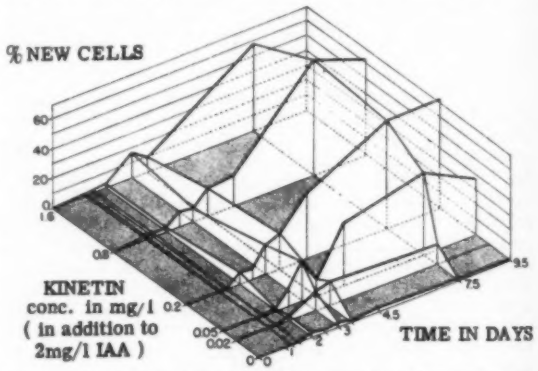

FIG. 5.—A specimen three-dimensional graph relating growth of cells in tissue culture to the concentration of kinetin in the medium. Reproduced by permission of the Editor of the *Journal of the National Cancer Institute*.

of kinetin in different concentrations on the growth rate of cells in tissue culture is beautifully shown in a manner which graphically reveals the relevant points. Having inscribed these enrichments on the capital of the second pillar (I trust they will not be regarded as excrescences), we must now proceed to the third.

ANALYSIS

By analysis we mean, of course, statistical analysis. There are those good practical men with no nonsense about them, for whom the word "statistics" is anathema, who quote

TABLE III.—*Method of Recording of Dependent and Independent Variables from Smyth and Bainbridge* (1957a)

	Forceps	Manual Removal	Toxaemia	Relative Disproportion	Breech	Occipito-posterior	A	B	C	D	E
							No. of Patients required for Valid Result	Significant Difference at 5% Level Patients			
								1,000	500	100	10
Forceps	213 9·16	6·6 19	7·5 6·8	15·9 53	13·6 63	11·7 42	54	1·38	2·29	5·64	18·2
Manual removal	14	75 3·23	12 3·8	1 2	8 13	3 3	158	0·84	1·40	3·46	11·15
Toxaemia	16	9	234 10·06	4·3 16	1·3 6·5	2·6 10	50	1·44	2·38	5·89	18·98
Relative disproportion	34	1	10	64 2·75	5 7	17 18	180	0·78	1·30	3·20	10·32
Breech	29	6	3	3	46 1·98		250	0·66	1·10	2·73	8·79
Occipito-posterior	25	2	6	11		60 2·58	194	0·76	1·26	3·10	10·00

the tag that "statistics can prove anything." Unfortunately, statistics have got to be used in nearly all clinical research, and it is better that they should be good statistics than bad. There is no need for the research worker in clinical medicine to have a knowledge of statistics, but it is an enormous advantage if he has, even though his knowledge of this subject is not very profound. To be able to do these things oneself, however, adds immensely to the interest and value of clinical research. Nevertheless, for the amateur, it would be wise to have the results checked by an expert, because it is fatally easy to make a gross error in a field in which one has not been bred. .

Finney (1956) has said: "That a high proportion of those whom I have broadly classed as experimenters should have a knowledge and appreciation of statistical principles is of great value to the progress of their science, but perhaps not so much because they are thereby enabled to do their own statistical work as because they understand better what needs to be done and what conclusions can reasonably be drawn."

Statistics have two roles in clinical research: they act either as a brake or as a headlamp. In the first role they prevent the experimenter from claiming as a consequence a result which may have emerged entirely due to chance—they prevent him, that is, from making a fool of himself. The most mistrustful cannot but applaud such an effect of a study which on the whole they view with suspicion.

Sometimes, however, statistics act like a headlamp and reveal a truth which could not have been apparent without such an analysis. When a result arrived at by a statistical analysis conflicts with common sense, then the statistics are probably wrong; when it conflicts with emotion, as in the relation between cigarette smoking and lung cancer, then this is not necessarily the case.

It must be admitted, however, that many research workers in the clinical field whose contributions are of great value have such an antipathy to manipulating the relatively simple formulae which the practice of statistical analysis demands that they must rely entirely on a professional statistician to do this for them. To get the best out of their results, however, they would be wise to plan their investigation in the first place in consultation with a statistician, one of whose qualifications is that he has mastered the science of the design of experiments. In this way material will not be wasted, and expense and labour will be saved.

"Analysis of Contaminants"

Granted all this, there is still one aspect of analysis which must be done by the investigator himself, and it is this operation which I have termed the "analysis of contaminants."

It must be presumed that in any investigation great care has been taken to avoid sources of error, but, however careful one may be, these are likely to creep in, and, having analysed the results, it is now necessary to go back over the sources of error and see how these may have influenced the conclusions. In describing a system for an analysis of contaminants or sources of error, I have discussed elsewhere (Atkins, 1957) the reasons for doing this at this stage, but it will be necessary to recapitulate some of these reasons here, because this part of the work can be done only by the investigator himself and cannot be left to the statistician.

If, for instance, we are investigating the effect of pregnancy on breast cancer in some primitive community, we would compare a series of women who had been pregnant with a series who had never been pregnant, in relation to the incidence of cancer. We will suppose that it is found that the incidence of breast cancer is higher in the "non-pregnant" series. In such an investigation three contaminants might be considered. The first arises because unmarried women might fail to reveal that they had been pregnant. This means that the allegedly "non-pregnant" series may have been salted, if that is the right word to use, with women who had in fact been pregnant. The effect of this contaminant would be to make the two series more alike than they should be; it would tend to favour a negative result to the investigation, and on that account it is referred to as a *negative* contaminant.

Furthermore, we might suppose, in a primitive community for instance, and indeed in this country up to a few years ago, that the possession of children ensured that the mother would be supported in her old age and would be more likely to live long enough to develop cancer of the breast. This contaminant, tending to lessen the positive difference between the "non-pregnant" and the "pregnant" series in relation to cancer, would also be a negative contaminant.

On the other hand, the fact that pregnant women are more likely to have suckled, and assuming, for the sake of argument, that suckling protected a woman from cancer of the breast, this contaminant would increase the difference between the two series and would on that account exaggerate the positive difference, and is therefore known as a *positive* contaminant.

Thus, a contaminant which tends to increase the greater or to decrease the less is a positive contaminant, and one which tends to do the reverse is a negative contaminant.

In the investigation which we have been considering we have assumed that analysis has revealed a positive result—namely, a significant difference between the two groups. It will be observed that the negative contaminants have tended to mask this significance, whereas the positive contaminant has tended to exaggerate it. If, on the other hand, an analysis had failed to reveal any difference between the two groups and that a negative result to the investigation was implied, then the negative contaminants would have strengthened this view and the positive contaminant would have weakened it. From this we may derive the general rule that contaminants bearing the opposite sign to the conclusion tend to conceal the conclusion and are, on that account, known as *inhibitory* contaminants; those bearing the same sign as the conclusion tend to exaggerate its significance and are on that account known as *illusive* contaminants. For a full discussion of this matter the reader is referred to the article quoted above, but it will be seen at once that the *illusive* contaminants are the treacherous ones, as they tend to make the investigator think that his results are more significant than they really are.

A paper giving an account of a clinical investigation, from which sources of error of this sort are inseparable, should contain—following the analysis—a formal statement of the inhibitory and illusive contaminants together with those which it is assumed do not affect the issue one way or the other and are known as *neutral* contaminants. In this manner the reader is able to assess the degree of confidence which can be placed in the investigation as a whole.

We have now completed our tour of the foundations of this edifice—clinical research. To establish these three pillars firmly on a bed of rock and to build on them requires a little extra thought and a great deal of additional careful work, but I believe in the end it will save future generations much labour and will prove far more enduring than the erection of a papier mâché façade to house some colourful exhibition on a foundation of sand.

I am grateful to Sir Charles Symonds for his helpful criticism.

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DEVELOPMENT OF HIRSUTISM AFTER PUBERTY*

BY

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[WITH SPECIAL PLATE]

The problem of the development of hirsutism after puberty is of great medical importance, and an understanding of its causes is therefore necessary. At the present time it seems that the condition may be divided into three main categories: (1) associated with adrenal cortical dysfunction of demonstrable proportions, such as that seen in the adreno-genital syndrome (Wilkins *et al.*, 1955) or in adreno-cortical tumours; (2) Stein-Leventhal syndrome; and (3) simple (idiopathic or constitutional) hirsutism. Much comment has been made on the last of these conditions (Dorfman and Shipley, 1956), whereas the Stein–Leventhal syndrome is much less known; even Stein accumulated only 75 cases in a period of 20 years (Stein *et al.*, 1949). The most popular view at present is that some androgenic substance may be derived from the ovary of these patients (Plate, 1951) and that theca luteinization is of importance in the ovarian pathology (Culiner and Shippel, 1949). In this communication emphasis is laid upon the problems of diagnosis and aetiology, including an examination of the biochemical features of the steroids found in the urine, both with and without stimulation of the adrenal cortex by corticotrophin.

Present Series

The cases here presented were all characterized by the development of hirsutism after puberty. Clinical analysis of the group (Table I) shows that it may be subdivided. The ultimate criterion for the diagnosis of the Stein–Leventhal syndrome was examination of portions of the ovaries after operation. In some instances the size of the ovary and appearance of the capsule were almost normal. Indeed, the impression is gained that only minimal enlargement, if any enlargement at all, need be present. In one instance the ovaries reached nearly three times normal size. Microscopically, persistent follicles were always identified, with a tendency to cyst formation, and proliferation and luteinization of the theca interna was present (Special Plate, Fig. 1).

TABLE I.—*Diagnostic Classification of Cases of Post-pubertal Hirsutism*

	No. of Cases
"Hirsutism" (? cause; previous encephalitis, 2)	32
Stein–Leventhal syndrome	9
? Stein–Leventhal syndrome	7
Adrenal virilism	1
Total	49
Adrenal cortical carcinoma	1

Indications for laparotomy in these patients have been sterility or severe menstrual irregularity associated with hirsutism, except in one instance where pain at menstruation was the immediate reason for operation. There have been clinical indications of at least a minor degree of ovarian enlargement. This evidence was obtained by vaginal examination with relaxation under anaesthesia, and confirmed, in all instances where it was done, by *x*-ray visualization after induction of pneumoperitoneum (Table II; Special Plate, Fig. 2). The dose of *x* rays involved is only 200 milliroentgens and has been considered negligible in the circumstances.

Examination of Table II will show that the patients with Stein–Leventhal ovaries were characterized by certain features, including the usual ones of sterility and menstrual irregularity. Ovulation, mental depression, and a family history of hirsutism were absent in comparison with the group designated as "hirsutism." This group of 32 patients remained after deducting those patients with other diagnoses as indicated in Table I. The group of patients designated as likely cases of Stein–Leventhal syndrome did not have a laparotomy performed. They were separated on account of their lack of fertility and their menstrual history, and otherwise resemble the Stein–Leventhal group.

TABLE II.—*Differentiating Features of "Hirsutism" and Stein-Leventhal Syndrome with Hirsutism*

	"Hirsutism"	Stein-Leventhal Syndrome	? Stein-Leventhal Syndrome
Total cases	32	9	7
Irregular menses	8	9	6
Sterility	2 (8)	6 (6)	2 (7)
Ovulation (temp.)	4 (4)	0 (3)	—
Vaginal examination under anaesthetic: positive results	6 (13)	9	3 (5)
Pelvic radiograph positive	2 (5)	6 (6)	? 1 (4)
Mental depression	10	1	0
Family history of hirsutism	7	0	1

Figures in parentheses in this and subsequent tables indicate number of patients observed where this was less than total in group.

Among the "hirsutism" group ovulation tended to be present. Of the six cases with suspicious ovaries as shown by vaginal examination, four had irregular menses and in one case normal ovaries were found on laparotomy. This was the only instance where laparotomy has been performed with negative ovarian findings. Of the two cases with possible ovarian enlargement as seen radiographically, one had irregular menses and the other was the patient mentioned with normal ovaries. Of the eight patients with irregular periods, two at least may have Stein–Leventhal ovaries, so that here is clinical evidence that even this group of patients may not be quite homogeneous. In Table III are presented the characters which appeared common to all groups. There was, and especially among the "hirsutism" group, a strong tendency for hirsutism to appear in the years just after establishment of menstruation. Somewhat surprisingly, obesity was equally distributed among the patients, and therefore seems not to be a useful indication of the possible presence of the Stein–Leventhal syndrome. It should be noted that one of the group of "hirsutism" patients had an enlarged clitoris, and this point will again be referred to below.

TABLE III.—*Features of Similarity in "Hirsutism" and Stein-Leventhal Syndrome*

	"Hirsutism"	Stein-Leventhal Syndrome	? Stein-Leventhal Syndrome
Total cases	32	9	7
Severe hirsutism	11	2	1
Age of onset of hirsutism (years)	11–35 (Under 18 in 19 patients)	12–24	12–24
Obesity	15	4	4
Acne	5	2	1
Enlarged clitoris	1	0	0
Hypertension	4	0	0

*Based on a communication given by F. T. G. P. at the Journée d'Endocrinologie de Marseille, May 9, 1958.

Studies of Urinary Steroids

Resting Excretion

The excretion of ketogenic steroids as determined by minor modifications of the method of Norymberski *et al.* (1953) was normal in all groups of patients. In the "hirsutism" group the mean 17-ketosteroid level was above the normal average of 10 mg., and significantly above the mean of the Stein–Leventhal group (P=0.05) and the "? Stein–Leventhal" group (P=0.01) (Table IV). It will be seen from the accompanying diagram that there was a wide scatter of 17-ketosteroid levels in the "hirsutism" group. These determinations were made by the techniques of Gibson and Norymberski (1954).

TABLE IV.—*Resting 17-Ketosteroids and Ketogenic Steroids*

	No. of Patients	17-Ketosteroids (mg. per day)	Ketogenic Steroids (mg. per day)
"Hirsutism"	32	*13·8*±0·61 (S.E.)	11·5±0·83 (25)
Stein–Leventhal syndrome	6	10·5±1·02 (P=<0·05)	8·9±1·08
? Stein–Leventhal syndrome	7	10·1±0·60 (P=<0·01)	11·4±1·27

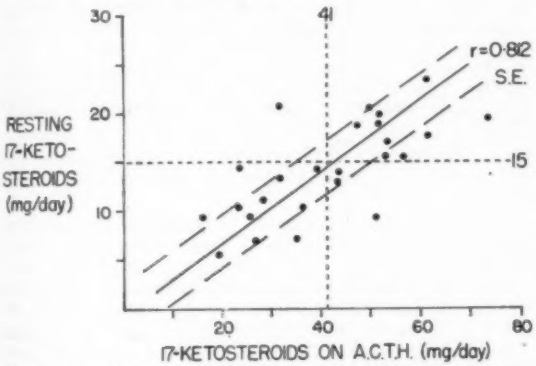

Diagram showing correlation between resting 17-ketosteroids and 17-ketosteroid response to four-day test with corticotrophin. The dotted lines indicate the upper normal ranges.

Response to Corticotrophin

Corticotrophin was injected in the form of gel in a dosage of 20 *U.S.P.* units intramuscularly twice daily for four days according to the method previously described (Prunty, 1956). Two batches of corticotrophin of known potency (89754 and P 80205) were used. The figures in Table V are the means of the highest figures reached during this test, usually those of the third or fourth day. The values for a control group of 15 women unaffected by hirsutism and of similar age are included. None of the patients under study differed from normal in the excretion of ketogenic steroids. The "hirsutism" group gave a mean for 17-ketosteroids significantly greater than normal (P=<0.01), and for the ratio ketogenic steroids/17-ketosteroids significantly less than normal (P=<0.01). The "? Stein–Leventhal" group gave a mean figure for 17-ketosteroids possibly significantly less than the "hirsutism" group (P=<0.05), but this was not true of the Stein–Leventhal group (P=>0.05). It should be emphasized that both these groups are small, as can be seen from the Table. A significant correlation was observed between the resting 17-ketosteroids and the level after corticotrophin injection in the "hirsutism" group (see Diagram).

TABLE V.—*Steroid Response to Corticotrophin*

	No. of Subjects	Ketogenic Steroids (mg. per day)	17-Ketosteroids (mg. per day)	Ratio Ketogenic Steroids/ 17-Ketosteroids
Controls	16	68·7±6·9 (S.E.)	*22·3*±1·95	*3·24*±0·30
"Hirsutism"	25	67·6±5·0	*40·4*±3·0	*1·80*±0·17
Stein–Leventhal syndrome	5	74·4±14·0	32·2±4·8	2·31±0·37
? Stein–Leventhal syndrome	6	65·2±15·3	*26·5*±3·2	2·36±0·43

Levels of significance for ketosteroid means: hirsutism/controls, P=<0·01; ? Stein–Leventhal syndrome hirsutism, P=<0·05; Stein–Leventhal syndrome/hirsutism, P=>0·05. For K.G.S./K.S. ratio, hirsutism/controls, P=<0·01.

Fractionation of 17-Ketosteroids

The resting urines of selected patients were extracted and the 17-ketosteroids fractionated according to the method of Brooks (1958), who gave data on six normal females aged 21–30. For this group the excretion of androsterone plus etiocholanolone amounted to 4.7±1.06 (S.D.) mg. per day. Three "hirsutism" patients excreted from 7.7 to 13.6 mg. per day, and two others 3.7 and 6.7 mg. per day respectively. Two Stein–Leventhal patients excreted 5.3 and 7.0 mg. and two "? Stein–Leventhal" patients 4.0 and 10.7 mg. per day. In spite of this elevation in some patients of all groups it will be seen from Table VI that the ratio of androsterone/etiocholanolone was within limits in all cases. Of the two Stein–Leventhal patients, in one the ratio was at the lower level of normal and in the other at the upper limit. The ratio 11-hydroxyandrosterone/11-hydroxyetiocholanolone was increased in the two patients with adreno-genital syndrome and in one each of those with Stein–Leventhal syndrome and suspected Stein–Leventhal syndrome. It is possibly increased (3.6) in one of the "hirsutism" patients. The separated 17-ketosteroids were divided according to their chromatographic properties into two groups—a less-polar and a more-polar group (Brooks, 1958). The former may be of extra-adrenal origin in part—for example, from the testes in men—and the latter comprise the 11-oxygenated ketosteroids of adrenal origin. In six normal females Brooks found a ratio of less-polar/more-polar of 4.89±0.95 (S.D.). The values for the Stein–Leventhal patients were well within this range (Table VI).

The excretion of dehydroepiandrosterone was increased in at least two of the "hirsutism" patients and in the two with adreno-genital syndrome. The data in Table VI for these two latter patients are taken from that of the case herein reported and from a pre-pubertal case recently examined by us.

Pregnanetriol Excretion

Urinary pregnanetriol has been determined by the method of Bongiovanni (1954), and in some instances confirmed by paper chromatographic separation. It is readily estimated and the importance of its estimation is considerable, for it is excreted in large amounts in the adreno-genital syndrome. It has been estimated in a group of cases, for the most part severely affected by hirsutism, where the possibility of the

TABLE VI.—*Fractionated Resting 17-Ketosteroids*

	No. of Subjects	Androsterone/ Etiocholanolone	11-Hydroxyandrosterone/ 11-Hydroxyetiocholanolone	Dehydroepiandrosterone (mg. per day)	Less-polar/ More-polar
Normal	6	1·31±0·45 (S.D.)	2·37±0·96	0·4±0·36	4·85±0·95
"Hirsutism"	5	0·8–1·8	2·1–3·6 (4)	0·7–1·7 (3) *2·2; 5·3* (2)	3·0–5·2 (5)
Stein–Leventhal syndrome	2	0·4; 2·1	1·9; *7·7*	0·2; 0·5	3·6; 3·7 (2)
? Stein–Leventhal syndrome	2	1·1; 1·4	3·0; 4·7	0·2; 0·7	3·0; 6·2 (2)
Adreno-genital syndrome	2	1·0; 1·7	*6·0; 5·0*	*3·6; 3·2*	3·0; 2·0 (2)

presence of the adreno-genital syndrome arose. In all three groups the values in some cases, when given corticotrophin, were above the level of 5 mg. per day which is tentatively considered to be the upper limit of normal. It is striking that in one of the "hirsutism" patients a level of 16.4 mg. was reached (Table VII).

In considering the interpretation of high levels of pregnanetriol the following points are of importance. In the adreno-genital syndrome the metabolic block in steroid synthesis leads to a deficiency of corticoid synthesis (Dorfman, 1954) and hence of the corticoid metabolites in the urine, with a parallel increase of pregnanetriol and related substances. Therefore under these conditions the ratio of pregnanetriol/corticoid metabolites will be very high in comparison with the normal. If the ketogenic steroid method here employed is used for the determination of the corticoid metabolites, pregnanetriol is also included in the estimate. Since the chromogenicity of this substance after oxidation is approximately 1, an idea of the amount of the corticoid metabolites (sufficient for our purpose) can be

TABLE VII.—*Pregnanetriol Excretion (mg. per day)*

	Response to Corticotrophin		
	Resting Pregnanetriol	Pregnanetriol	17-Keto-steroids
"Hirsutism":			
4 patients	0·8–1·8	2·4–4·8	31–52
3 ,,	1·1–2·7	*7·6–16·4*	36–74
Stein–Leventhal syndrome:			
2 patients	1·7–1·8	4·4–5·6	16–40
2 ,,	1·4–2·6	*6·9–10·3*	27–37
? Stein–Leventhal syndrome:			
2 patients	2·6 1·0–2·9	2·4–*6·0*	17–38

obtained by subtracting the value for pregnanetriol from the figure for ketogenic steroids. Under normal circumstances the ratio is 1/10, but we have found that in the adreno-genital syndrome the value for pregnanetriol can even exceed that for ketogenic steroids, giving an apparent ratio of infinity. On direct determination by chromatography the resting ratio pregnanetriol/tetrahydrocortisone in the case in Table VIII is 6/1. Under normal circumstances, from data given by Prunty (1956) and by de Courcy *et al.* (1953), it should be in the neighbourhood of 1/3. This finding is therefore in agreement with the above conclusion.

Returning now to the question of the high values observed for pregnanetriol in some of the "hirsutism" cases given corticotrophin (Table VII), determination of the ratio pregnanetriol/(ketogenic steroids − pregnanetriol) in response to corticotrophin shows the values to fall between 1/6 and 1/8, and for the Stein–Leventhal syndrome between 1/9 and 1/13. It is therefore justifiable to conclude that the production of corticoid metabolites was good in these cases in response to corticotrophin, and that the degree of any metabolic block, if present, is of a much lower order than in the true adreno-genital syndrome.

Adreno-genital Syndrome and Carcinoma of Adrenal Cortex

It has been stated that one of the series of 49 cases of hirsutism developing after puberty is considered to be a true example of the adreno-genital syndrome. The features of this case are given in Table VIII. Apart from these it was noted that the patient was short in stature and union of her bony epiphyses had occurred. The main features of her steroid pattern have been indicated above. The resting value for 17-ketosteroids and their response to corticotrophin, although elevated, lie within the limits of the patients with hirsutism. The raised value of the ratio 11-hydroxyandrosterone/11-hydroxyetiocholanolone (Table VI) conforms with the metabolic block in corticoid synthesis, and the elevation of dehydroepiandrosterone in many of these cases is well recognized (Broster *et al.*, 1953).

The patient with adrenal carcinoma has been included as an example of a further cause for development of post-pubertal hirsutism, and data for this patient are also given

TABLE VIII.—*Details of Case of Adreno-genital Syndrome and Case of Carcinoma of Adrenal Cortex*

	Case of Adreno-genital Syndrome	Case of Carcinoma of Adrenal Cortex
Age	18 years	21 years
Onset	14 ,,	17 ,,
Menses	Regular	Regular
Clitoris	Enlarged	Enlarged
Ovulation	+	
Ovary size	Normal	
Obesity	None	None
Acne	Moderate	Moderate
17-Ketosteroids	14·8–20·8 mg. per day	29·8 mg. per day (β fraction 1·2 mg.)
Ketogenic steroids	10·6–19·0 ,, ,,	
Pregnanetriol	11·7 ,, ,,	
Pregnanetriol/tetrahydrocortisone	6/1	
Response to corticotrophin:		
17-Ketosteroids	46 mg. per day	
Pregnanetriol	54 ,, ,,	

in Table VIII. Here it is important to emphasize that elevation of the 17-ketosteroid level was not great enough to arouse high suspicion of the presence of carcinoma, and, as judged by assay of the β-ketonic 17-ketosteroid fraction, dehydroepiandrosterone excretion was not increased (data from Prunty, 1950; see also Dorfman and Shipley, 1956). By chance a definite pre-operative diagnosis of adrenal tumour was made possible by *x*-ray examination (Special Plate, Fig. 3); a small tumour with an accompanying calcified thrombus containing tumour cells was outlined above the left kidney simultaneously shown up by intravenous pyelography. The tumour, which weighed 23 g., was removed, but leaving some of the cells in the adrenal vein. Great improvement occurred in the patient's symptoms, and she is known to have survived longer than 10 years (Prunty, 1944).

The presence of enlargement of the clitoris in these two patients should be emphasized as indicating a greater degree of virilization than that occurring in the "hirsutism" group. It is true that one of the patients in this group (Table III) also had enlargement of the clitoris, but insufficient information was available at the time to establish whether she too had the adreno-genital syndrome; she showed a partial degree of improvement after subtotal adrenalectomy.

Gonadotrophin Excretion

Through the kindness of Dr. J. A. Loraine, of Edinburgh, quantitative estimations of the "total" gonadotrophin in the urine of two patients from each of the major groups has been made. The values reported in Table IX are expressed

TABLE IX.—*Gonadotrophin Excretion (H.M.G. units per day)*

	First Patient	Second Patient
"Hirsutism"	6	7
Stein–Leventhal syndrome	<10	6
? Stein–Leventhal syndrome	5	5

as units of the provisional standard H.M.G.−20A (1 unit equals 1 mg.). The method used was that of Loraine and Brown (see Loraine, 1958). All the values here reported are normal and do not differ from one another.

Discussions

From the clinical point of view the surprisingly high incidence of the Stein–Leventhal syndrome in the group of patients presenting with hirsutism is of special interest. The accompanying menstrual disturbance and sterility were important. Mental changes were much less frequent than in the other patients. The degree of ovarian enlargement in no case reached the dimensions given by Stein *et al.* (1949) as being commonly present. The importance of minimal ovarian enlargement must therefore be stressed.

Somewhat surprising was the normal menstruation of the patients with, respectively, adreno-genital syndrome and adrenal carcinoma; the former was also known to ovulate. The nature of the lesion in the adreno-genital case is of interest. The biochemical abnormality appeared to be that typical of the common pre-pubertal adreno-genital syndrome. However, menstruation, even with ovulation, is unusual in such patients when they reach puberty, and all the signs in our patients developed after puberty. It has been noted that the patient was short in stature, and this might possibly be the only indication that the adrenal condition could have been present before puberty. Recently Blizzard and Wilkins (1957) made brief mention of a case in which the condition apparently developed after puberty.

Many of the existing reports on hirsutism in the literature may be biased by the heterogeneity of clinical material and, in the case of observations on steroid metabolism, by the non-specificity of the methods used. In the present observations on steroid fractionation most of the necessary hydrolysis was performed by the use of glucuronidase (Brooks, 1958), so that artifact formation was minimized and specific chromatographic separation of the compounds was made. The levels of ketosteroids found agree with the elevation of values reported in some cases of hirsutism and with the majority of normal values in the Stein–Leventhal syndrome (Dorfman and Shipley, 1956; Jailer and Vande Weile, 1954). Ten of the 25 cases of hirsutism exceeded the normal range, both for resting 17-ketosteroids and in response to corticotrophin (see Diagram). This tendency for increased response to corticotrophin in 17-ketosteroid excretion is reflected in the low ratio ketogenic steroids/17-ketosteroids for the "hirsutism" group (Table V) previously reported by Prunty (1956), and has been commented on by Nabarro *et al.* (1958). It seems one indication that some alteration of adrenal androgen secretion might occur in these patients.

The ovarian secretion of an androgen such as testosterone, as suggested by Plate (1951), might be evidenced by changes in the ketosteroid fractions, although as testosterone itself, for instance, is a potent androgen the amounts secreted could perhaps be too small to affect the results very significantly. Administration of testosterone to human subjects has given widely varying results for the ratio of androsterone/etiocholanolone (0.3–3.4), depending upon the conditions (Fukushima, Dobriner, and Gallagher, 1954; Fukushima, Bradlow, *et al.*, 1954; Rubin *et al.*, 1954), so that little may be deduced in this respect from these experiments. No definite abnormality has emerged from the present observations. The secretion of an androgen such as testosterone not metabolized to 11-oxygenated C_{19} steroids should raise the ratio of less polar/more polar ketosteroids. This was not observed to occur in two patients with Stein–Leventhal syndrome. It has, however, been noted in two male patients studied by Brooks (1958), the values being 8.8 and 7.9 owing to an increased less-polar fraction. Calculation of the corresponding ratio from the data of Rubin *et al.* (1954) shows a similar ratio to ours for females, but there was no increase for males. The significance of changes in the ratio 11-hydroxyandrosterone/11-hydroxyetiocholanolone has previously been discussed by Brooks (1958). Its increase is recognized in the adreno-genital syndrome and is to be expected. The significance of the rise in this ratio in the Stein–Leventhal and "? Stein–Leventhal" patients requires further study.

The behaviour of pregnanetriol excretion in these patients resembled that of the "hirsutism" patients and not that of the adreno-genital syndrome. The results of the gonadotrophin assay do not lend support to the idea that there is a large increase of luteinizing-hormone production in the Stein–Leventhal syndrome. So far as they go the observations do not give support to the view that there is, by the methods used, a detectable increase of ovarian androgen in the Stein–Leventhal patients, but there are indications from the present work that alterations in adrenal secretion can also occur in this syndrome.

Summary

Clinical observations on a group of 49 women developing post-pubertal hirsutism indicate the importance of sterility and menstrual disturbance in the Stein–Leventhal syndrome. Ovarian enlargement may be minimal.

Further evidence for an increase in adrenal ketosteroid excretion in a large proportion of patients with hirsutism is presented, and the biochemical distinction of these cases from the adreno-genital syndrome discussed.

Limited observations have given no definite indication of increase of an ovarian androgen metabolized to 17-ketosteroids in the Stein–Leventhal syndrome, nor of any large increase of luteinizing-hormone production.

The somewhat unobtrusive occurrence of an adrenal cortical carcinoma as a cause of post-pubertal hirsutism and a probable instance of post-pubertal development of the adreno-genital syndrome are presented.

We are indebted to our colleagues in the Department of Obstetrics and Gynaecology, especially to the late Dr. K. Bowes, to Dr. J. W. McLaren, head of the Department of Radiology, and to Dr. R. G. Shorter, in the Department of Clinical Pathology, St. Thomas's Hospital, for their co-operation.

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The terms of reference of the Food Standards Committee have now been revised. The Committee was set up in 1947 to advise Ministers on regulations to control the composition of food for the protection of consumers. The revised terms of reference are as follows: "To advise the Secretary of State for Scotland, the Minister of Agriculture, Fisheries, and Food, the Minister of Health, and as respects Northern Ireland the Secretary of State for the Home Department, on the composition, description, labelling, and advertising of food, with particular reference to the exercise of the powers conferred on Ministers by Sections 4, 5, and 7 of the Food and Drugs Act, 1955, and the corresponding provisions in enactments relating to Scotland and Northern Ireland." The new terms of reference give the Committee more scope to consider and recommend on the control of food labelling and advertising; previously the Committee could deal with the labelling only of foods for which standards of composition were prescribed. Another change is that liquid milk is no longer excluded, but the Committee will not deal with any aspect of milk until the Committee on the Composition of Milk has reported.

RELIEF OF DEAFNESS BY STAPES MOBILIZATION

BY

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[WITH SPECIAL PLATE]

One of the greatest advances in the whole realm of otology of this century has been the perfection of the fenestration operation for the relief of otosclerotic deafness, and an interesting twist in the history of medicine is the fact that this elaborate surgical ritual should have been largely replaced by a manipulation so obvious and so seemingly simple as to be deemed in some quarters an "office procedure." It is also of interest to note that our forebears of the last century, in their attempts to alleviate deafness, turned their attention first to the stapes, and it was probably Kessel who carried out the first mobilization in 1875. Kessel gives a fascinating description of how in one case he freed the stapes, with a gratifying improvement in hearing, but with no relief from the tinnitus which was the patient's main complaint. On the following day he divided the stapedius tendon, and ultimately it was found that not only had the hearing improvement been maintained but the tinnitus cured (Kessel, 1876). During the ensuing 25 years further attempts either to mobilize or to remove the stapes were made, and these pioneering operations were associated with the names of Miot (1890), Boucheron (1888), and Faraci (1899) in Europe and Blake (1891, 1892, 1893), Jack (1891, 1892, 1893a b, 1894), and Burnett (1893) in America.

The usual method was to approach the middle-ear cavity by incising the tympanic membrane rather than by reflecting it. Illumination was poor, and to the best of our knowledge no use was made of magnification—an adjunct which is to-day considered essential to the proper execution of the later stages of the operation. Notwithstanding such severe handicaps, large numbers of these operations were performed—more, in fact, than is generally realized—and Miot alone in 1890 published no fewer than 200 cases. It is therefore rather a mystery that at the turn of the century the sun should have gone down on stapes surgery, not to rise again for 50 years. It might be assumed that post-operative infection was responsible for bringing the technique into disrepute, for there were no guardian angels in the form of antibiotics to protect the patient's life and the surgeon's reputation; but it would seem that even in the absence of antibiotic "cover" serious post-operative complications did not occur. It is possible that the fear rather than the actual fact of intracranial complications was partly to blame, for such complications, which occurred frequently in the course of chronic middle-ear suppuration, often defied all attempts at treatment and terminated fatally. The relentless progress of these grim complications from stage to stage was well known to the general public, and they acquired a sinister reputation which persists to-day in spite of their rarity. Moreover, at the end of the last century the attitude of several distinguished otologists was unfavourable to the natural development of temporal-bone surgery in non-infected cases, and it was indicted for numerous reasons, many of which were invalid.

Samuel Rosen in 1952 rediscovered the operation when testing the stapes for immobility under local analgesia (Rosen, 1953). It is said that the discovery was accidental, and great credit is due to him for his observation and perseverance, and for launching a method of relieving deafness which was destined to have such an impact on otology.

Indications for Stapes Mobilization

(1) The operation is most commonly indicated in cases of otosclerosis in which fenestration would have been advised formerly, and the various criteria on which the decision for that operation was based have been repeated on numerous occasions during the last 20 years. To recapitulate briefly, the diagnosis of otosclerosis should be firm and the hearing loss reasonably symmetrical. Pure-tone audiometry should ideally show a 35-55 decibel loss of air-conduction for the critical speech frequencies, with a satisfactory air-bone gap (preferably at least 20 decibels). Amplification should be well tolerated, paracusis present, and Schwartze's sign absent.

(2) Early cases of otosclerosis which hitherto would not have been subjected to the fenestration operation on account of its magnitude are suitable for stapes mobilization. In the past it was the usual practice to examine these cases at intervals of six or twelve months with the intention of advising operation when the hearing reached a level low enough to render a major surgical procedure worth while. This management, however, was not entirely free from objections. Patients would move and become lost from the follow-up, or would be inveigled into purchasing a hearing-aid (usually unsuitable, unwelcome, and very expensive), or, worst of all, would arrive for audiometry at the appointed time only to show a serious and inexplicable hearing loss placing them in the category of late and unsuitable cases.

(3) Late cases of otosclerosis have in many circumstances been regarded as unsuitable for fenestration. The perceptive element of the deafness may reduce the possible theoretical gain in hearing to such a level as to necessitate the wearing of a hearing-aid post-operatively. Obviously, it is of dubious value to subject the patient to a major operation giving but little hope of dispensing with an appliance but at the same time producing an operation cavity in which it may be impossible to wear that appliance. Stapes mobilization, however, in the same patient is a different proposition. There is a chance that it may permit the instrument to be discarded, but in the event of failure an aid may continue to be worn, even in the operated ear.

Finally, there is the very late case in which a powerful aid gives insufficient amplification, and here also the stapes operation is feasible, for it may improve the hearing sufficiently to enable the patient to obtain benefit from an aid.

(4) Unilateral cases of otosclerosis with good hearing in the contralateral ear have seldom, in my opinion, justified fenestration. The over-all subjective improvement is disappointing when the hearing level of a deafened ear is raised, provided the other ear is normal, and, though a dramatic difference may be shown audiometrically, the patient is seldom enthusiastic. Nevertheless, it is certainly most desirable that the hearing in both ears should be symmetrical, and stapes mobilization is without doubt justified in an endeavour to achieve this state.

(5) Patients suffering from conduction deafness caused by adhesions following serous otitis media are suitable for exploration of the tympanic cavity by the techniques of Lempert and Rosen. For many years the management of this type of deafness consisted of repeated politzerization or eustachian catheterization, involving the patient in great loss of time and not a little suffering, the net result being in most cases a minor and transient improvement in hearing. In recent years these methods of treatment have been used less and less, partly because their limitations are appreciated, and also for the reason that conduction deafness due to causes other than otosclerosis is seen less frequently than

hitherto owing, no doubt, to the increased care of the upper respiratory tract in childhood and to the introduction of antibiotics. Nevertheless these cases are seen in moderate numbers, and the technique of stapes surgery opens a new vista in their investigation and treatment.

(6) Lastly, the techniques referred to provide a direct and safe method for inspecting the tympanic cavity and for carrying out curative procedures in obscure cases of deafness the precise diagnosis of which may be in doubt prior to operation. These include such conditions as round-window otosclerosis (McLay, 1957) and traumatic ossicular dislocation (Gisselsson, 1958).

Technique

Anaesthesia

The operation is most commonly performed under local analgesia, which carries distinct advantages. The hearing may be tested at all stages, and the achievement of a mobile stapes is immediately verified by the hearing improvement obtained, thus obviating any manipulation which might be unnecessary and traumatic. Many persons in Great Britain, however, have a deep antipathy towards local analgesia whilst being perfectly happy to undergo general anaesthesia, thanks no doubt to the high degree of perfection to which the latter has been raised by anaesthetists. It is my belief that such patients should not be denied the operation, but should be given a general anaesthetic, under which extremely good results may be obtained. Some surgeons, in fact, prefer general anaesthesia as a routine, as it gives them freedom of movement and freedom of speech (!) (Venters, 1958).

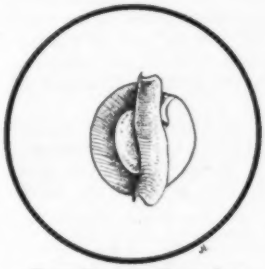
Premedication consists of pethidine, 100 mg. intramuscularly, and atropine, 1/100 gr. (0.65 mg.) subcutaneously, and is given 45 minutes beforehand. No shaving of hair or other local pre-operative preparation is necessary, but the meatus is carefully inspected on the day before operation in order to ensure the absence of cerumen or any inflammatory condition. After swabbing of the meatus and pinna with flavine 1:1,000 in 50% spirit, "xylotox" 2% with adrenaline 1:80,000 is injected at several points under the skin of the meatus at the junction of the osseous and cartilaginous parts of the latter. Only 1-2 ml. is used, and the extreme degree and widespread analgesic effect of this small quantity is surprising. It has not yet been my experience for the patient to complain of pain at any stage of the operation, apart from the initial needle prick. (Special Plate, Figs. 1 and 2.)

Operative Details

The incision is derived from that of Lempert for tympano-sympathectomy (Lempert, 1946), but differs slightly in position, being made from 12 o'clock to 6 o'clock in the skin of the posterior meatal wall. Its upper and lower extremities are 2 mm. from the edge of the tympanic membrane, but its centre portion is at least twice this distance. (Special Plate, Fig. 3; Text Fig. 1.) The most useful instrument for making the incision has proved to be one of Rosen's bone spoons which is sharpened before each operation until a knife-edge is obtained. This was suggested to me by McKenzie (McKenzie and Rainer, 1957) and has also been mentioned by Simson Hall (1958).

TEXT FIG. 1.—Incision in meatal wall.

The collar of skin medial to the incision is now gently raised from the underlying bone until the edge of the tympanic membrane can be lifted from its sulcus, exposing underlying mucous membrane. The latter is pierced with a sharp seeker, which serves to divide it in the line of the annulus tympanicus, and at this stage a large air-bubble invariably appears from the middle-ear cavity (Special Plate, Fig. 4; Text Fig. 2.) The posterior part of the tympanic membrane may now be folded forwards across the manubrium of the malleus, exposing the middle-ear cavity (Plate, Fig. 5; Text Fig. 3.) This first stage is very laborious, and must be executed with extreme caution in order to avoid tearing the tympano-meatal flap at the junction of the tympanic membrane with the delicate skin of the posterior meatal wall. In many cases the incudo-stapedial joint is now clearly seen, with the stapedius tendon and chorda tympani (Plate, Figs. 5 and 6; Text Fig. 4), but in some cases these structures are partly hidden by overhanging annulus tympanicus, which must be removed with Rosen's curette or Lempert's fenestration curettes (Text, Fig. 5).



TEXT FIG. 2.—Entry into tympanic cavity.

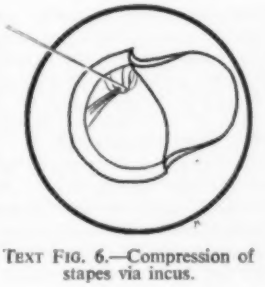
TEXT FIG. 3.—Incudo-stapedial joint and stapedius tendon.

TEXT FIG. 4.—Incudo-stapedial joint, stapedius tendon, chorda tympani, and round-window niche.

TEXT FIG. 5.—Removal of part of tympanic ring.

At this juncture it is desirable to employ increased magnification if, as is often the case, the first stage has been carried out with the aid of a binocular loupe magnifying two diameters. The Zeiss operating microscope gives a large choice of magnifications, but for the preliminary steps in mobilization 10 or 16 diameters are adequate.

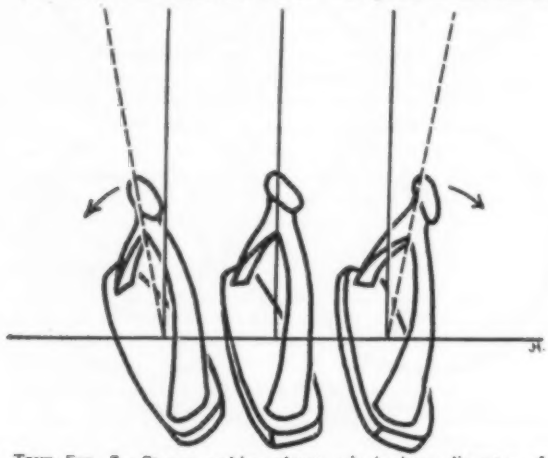
The stapes may now be tested for mobility, after which mobilization should be attempted, starting with manœuvres as atraumatic as possible, and in the event of failure passing on to manipulations involving greater forces. The reason for this orderly sequence is that the degree of fixity of the stapes varies from case to case, and it is obviously better to achieve mobilization with the minimum risk of trauma to the middle and internal ear structures. The first and least traumatic manipulation, which is perhaps most closely parallel to normal physiological movement, is the transincudial method advocated by Goodhill (1955), House (1957), and Scheer (1958). The point of the seeker is firmly planted in the tip of the long process of the incus and pulsating pressure is exerted towards the oval window, compressing the stapes from head to footplate (Text Fig. 6). In a



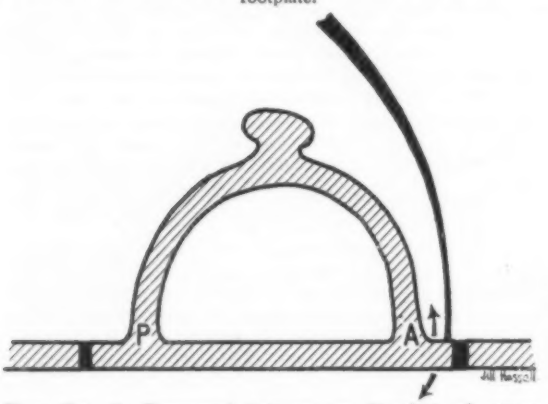
TEXT FIG. 6.—Compression of stapes via incus.

small proportion of early cases mobility is effected, but only minimal pressure may be permitted or the stapedial crura might be fractured or driven through the footplate, and it is usually necessary to pass on to the second manœuvre. (Text Fig. 7). This consists in attempting to rock the stapes from side to side in the axis of the long diameter of its footplate and is advocated by McKenzie and Rainer (1957); but the forces acting here are at right-angles to those when Rosen's original method of pressure on the anterior aspect of the stapedial neck is employed. My third manœuvre is to attempt mobilization by downward pressure on the small lip of footplate which sometimes projects well in front of the anterior crus (Text Fig. 8); and, fourthly, to endeavour to prise the footplate loose in the manner described by Rosen (1955).

If all these methods fail, it is probable that further attempts at mobilization would fracture the stapedial crura, and it is advisable to proceed to Rosen's method of footplate fenestration (Rosen, 1956). The point of the instrument used, which resembles a crochet hook, is inserted with extreme care through the footplate to a depth of not more than 1 mm., and on withdrawal brings away a small portion of bone, permitting the escape of a little perilymph. It is needless to stress that the footplate technique requires movements of precision which can be safely controlled only under high magnification.



TEXT FIG. 7.—Stapes rocking about axis in long diameter of footplate.



TEXT FIG. 8.—Downward pressure on footplate of stapes anteriorly.

In the conscious patient the hearing is tested from time to time, and there is usually little doubt when mobilization has been achieved, for the hearing improvement is sometimes dramatic and is enhanced by replacement of the tympanic membrane. "Gelfoam" provides a suitable dressing, and may be retained in position by a strip of ¼ inch (6.4 mm.) ribbon gauze. Simson Hall (1958) places a small piece of oil-silk in contact with the tympanic membrane in order to lessen the risk of perforation—a method which would seem to be most advantageous, as the oil-silk may be left for a considerable time should a healing perforation be suspected, and will act as a perfect splint.

Post-operative Care

As a rule no particular sedation is required; the ribbon-gauze strip is removed after two to four days, and the patient is usually discharged on the fourth or fifth post-operative day. Penicillin is given regularly during this time. It is often found that the immediate improvement in hearing is temporarily lost, and it is wise to warn the patient that this is merely due to an accumulation of debris in the meatal canal and that the initial hearing improvement will almost certainly return when this clears. The debris usually separates and is extruded without assistance, and manipulations should be avoided so far as possible at the post-operative attendances.

If at the time of operation a successful outcome is expected but post-operative testing reveals no improvement in the hearing, a further exploration with attempted mobilization may be made at a later date. There is no contraindication to a repetition of the same technique; in fact, the exposure is often achieved more readily the second time. In the event of repeated failure, fenestration is advised if the case is considered suitable for this operation, and the fact that the patient has been the subject of one or more attempts at stapes mobilization in no way impedes the fenestration technique or reduces the chances of a successful outcome.

It may be of interest at this stage to collate certain aspects of the two operations—fenestration and stapes mobilization.

	Fenestration	Stapes Mobilization
Usual sojourn in hospital	2–3 weeks	3–5 days
Length of operation ..	1½–3 hours	1/3–1 hour
Anaesthetic	General (in U.K.)	Local or general
Post-operative vomiting	Occasional	Nil
,, vertigo ..	Variable	Rare
,, pain ..	Occasional	Slight
,, otorrhoea	Not uncommon. May be intractable	Rare
Indications	Limited	Wide
Possibility of repeating operation in the event of failure	Revision difficult and hazardous, and seldom meets with lasting success	Operation can be repeated on same ear two or three times. Ultimately possible to fenestrate ear
Post-operative attendances	May be frequent if operation cavity becomes infected	Occasional

Complications

A search of the literature reveals that very few complications are reported, the most common complication occurring during operation and consisting of a fracture of the anterior crus or of both crura of the stapes. This is met by abandoning any further attempts at mobilization and proceeding straight to footplate fenestration. Occasionally tears occur in the tympanic membrane, but these seldom result in permanent perforations. In the first 50 cases operated on at Westminster Hospital one small perforation persisted, but the tympanic membrane was subsequently repaired by myringoplasty. There were also in this small series four cases of acute otitis media which occurred after the patients had been discharged from hospital, but the infection responded rapidly to antibiotic treatment in each case. In some series transient facial pareses, which have cleared up completely as soon as the effect of the local analgesic agent has passed off, have been reported.

It might be thought that complications would be likely to follow invasion of the sanctum of the inner ear by the footplate manœuvres described, but Rosen (1958) reports that in over 200 footplate fenestrations there was not a single instance of labyrinthitis or involvement of the facial nerve.

Results

It is notoriously difficult to depict the results of a procedure designed to improve the hearing. Pre-operatively the patients fall into different categories as regards their suitability for operation and the amount of improvement which might be expected to accrue therefrom, so it is obviously invidious to compare the results obtained in one group with those in another unless the original pre-operative category of the patient is borne continually in mind. Pure-tone and even speech audiometry sometimes give a misleading picture which does not in every case correspond with the subjective sensations of the patient. Finally, the terms used by surgeons in describing improvement or deterioration, success or failure, though having an exact significance to their authors, do not always convey the same meaning to their readers.

Scheer (1957) found that the operation had resulted in the restoration of practical and functional hearing in 36% of cases, but later (Scheer, 1958), by including the footplate techniques, was able to obtain an acceptable hearing improvement in 75–80% of cases. Rosen (1958) in an analysis of 254 cases states that a significant improvement in hearing was obtained in 77%. Venters's (1958) initial successes (including "very successful" and "moderate") reached 70%, and the number maintained for six months or more 53%. It would seem that many surgeons find that of all their cases subjected to operation approximately one-third obtain a great, and in some cases dramatic, improvement in hearing; approximately one-third are improved, but to a lesser degree; whilst the remainder are scarcely affected. Of the first 50 cases operated upon at Westminster Hospital (admittedly a small number), 29 have shown a useful, and in some cases very great, improvement in the hearing, 11 have been moderately improved, and in 10 cases the hearing has remained unchanged. It is likely that in the course of time a few of the 29 "very successful" cases of the first 50 will deteriorate and enter other categories, so the eventual ratio of great improvement: slight improvement: no change may not be very far from 1:1:1.

Of extreme importance is the problem of the duration of improvement in terms of years. Rosen (1958) states that over 95% of the improved cases have maintained their hearing improvement, without regression, for periods of up to five years, and it is worthy of note that his first case, operated on in April, 1952, had at the time of reporting maintained his hearing improvement for 4 years 10 months.

Summary

The history of stapes mobilization is traced from the 1870's. After a dormant period of half a century the operation was resurrected by Rosen in 1952.

The indications for the operation are given, and it is noteworthy that stapes mobilization is more general in its application than fenestration of the labyrinth.

The technique is described. Local analgesia is preferred, but is not obligatory. After the incudo-stapedial joint and surrounding anatomical structures have been displayed, manœuvres aimed at freeing the stapes are carried out. If mobilization is found to be impossible, fenestration of the stapes footplate is undertaken. The progress of the operation is controlled by hearing tests at intervals.

The post-operative care is mentioned, and a comparison between features of stapes mobilization and fenestration shows that when such matters as length of stay in hospital and post-operative discomfort, etc., are considered the magnitude of the former operation is much less than that of the latter.

Results to date suggest that, of the patients undergoing the operation, approximately one-third may be expected to obtain a useful, lasting, and in some cases great hearing improvement, one-third a slight improvement, and one-third no improvement. In cases in which the result is disappointing, the fact that the operation may have been performed several times does not preclude a patient from undergoing fenestration of the labyrinth at a later date.

I thank Dr. Peter Hansell and Miss Jill Hassell of the Department of Medical Photography of Westminster Hospital for the illustrations.

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FAMILIAL HAEMOPHAGOCYTIC RETICULOSIS

BY

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[WITH SPECIAL PLATE]

The title "familial haemophagocytic reticulosis" was given by Farquhar and Claireaux (1952) to an unusual disorder which affected the first two children of a family. Both infants had developed anorexia, vomiting, irritability, and pallor at the age of 9 weeks. Both had enlargement of the liver and spleen, and both had progressive anaemia, leucopenia with profound granulopenia, and thrombocytopenia. Smears of the peripheral blood always contained a high percentage of unrecognizable damaged cells and a small proportion of atypical mononuclear cells bearing some resemblance to those occurring in glandular fever. The first baby, a male, died at the age of 10 weeks. Clinical investigation of the second infant, a female, failed to reveal the cause of the pancytopenia. In particular, there was no evidence either of erythroblastosis foetalis or of exposure to drugs or poisons. The resistance of the red blood cells to hypotonic dilutions of saline was normal,

and the marrow was always richly cellular and normoblastic. Radiographs of the skeleton failed to reveal any sign of reticulo-endotheliosis. This infant appeared to respond temporarily to corticotrophin, but the improvement was not maintained and she died at the age of 22 weeks.

Necropsy revealed in both children a remarkable proliferation of histiocytes throughout the reticulo-endothelial system. This had not been apparent in the ante-mortem marrow smears. The histiocytes contained very many ingested red cells and less numerous white cells. The picture was not that of Letterer–Siwe's disease, and a suggestion that it might be identical with histiocytic medullary reticulosis was later refuted by Marshall (1956).

The third child of the family, a girl, was mentioned by the authors. She was normal clinically at birth, but smear cells were numerous in the peripheral blood films. A high percentage of atypical large lymphocytes appeared in the blood between the sixth and eighth weeks of life, and at the age of 10 weeks she developed severe anorexia. Neither liver nor spleen was palpable, but she had a mild anaemia, and the atypical lymphocytes persisted in the blood until she was 18 months old. She became no worse clinically, however, and when she was last examined at the age of 4 years 4 months the haemoglobin level and white-cell picture in the blood were found to be normal. She is now reported by her parents to be an apparently healthy 5-year-old.

The results of serological investigation of these children, the fourth child, the parents, and the paternal grandparents are given in the Table. Positive reactions to Coombs's test were reported in blood from Cases 2 and 3 and from the father. On the father Coombs's test on a later occasion gave a negative result. The paternal grandmother's test was in doubt, and she refused further investigation, possibly because she suspected the discovery of a discrepancy between the genotypes of her son and her husband (see Table) indicating that they were not blood relations. No abnormal antibodies against a wide range of known blood groups (including MNS, P, Lewis, Lutheran, Kell, Duffy, and Kidd) could be found in the mother's blood after the birth of the second child. Her serum was tested by the indirect Coombs method against the cells of the paternal grandparents with negative results.

Table Showing Results of Serological Tests on Members of the Family

Subject	Date	Genotype		Coombs's Test	Other Comments
		ABO	Rh		
Case 1 ..	3/7/50	O	Negative	Negative	
Case 2 ..	19/9/51	O	CDe/cde	Positive	
Case 3 ..	12/9/51	O	Positive	Negative	
	25/9/51	O	,,	,,	
	13/10/52	O	,,	,,	Trace of cold agglutinins
	14/11/52	O	,,	,,	No evidence of cold agglutinins
	18/3/53	O	,,	Weak positive	,, ,,
	29/5/53	O	,,	Negative	
	16/3/54	O	,,	,,	,, ,,
Case 4 ..	30/12/55	O	Negative	Negative	
	5/3/56	O	,,	,,	Well-marked platelet agglutinin
	9/5/56	O	,,		
	22/5/56				Post-splenectomy. Strong platelet agglutinins
	29/5/56	O	,,		
Father ..	19/9/51	O	cDE/cde	Positive	
	1/12/56			Negative	
	5/1/57			,,	
Mother ..	19/9/51	O	CDe/cde	Negative	
	1/12/56			,,	
	5/1/57			,,	
Paternal grandfather	2/10/51	O	CDe/CDe	Negative	
Paternal grandmother	2/10/51	O	cde/cde	Doubtful weak positive	Refused further investigation

Although the parents had asked that the third pregnancy should be terminated shortly after conception had taken place, and this had been refused, they were so encouraged by the apparent health of this child that they decided to have more children. The object of the present paper is to present the clinical, haematological, and pathological findings in the fourth child (Case 4), and to record the results of further investigations of the parents. On the basis of these new data an attempt is made to discuss the nature of the disorder.

Details of Case 4

The baby, a male, was born outside Edinburgh. His blood picture was normal and the result of Coombs's test negative. When 14 weeks old he developed anorexia and irritability followed by pallor. He was admitted to the Royal Edinburgh Hospital for Sick Children four weeks later (Fig. A). Both liver and spleen were firmly enlarged. His haemoglobin was 65% (Sahli; 100% = 14.8 g.) and the total white cell count was 2,500 per c.mm. The peripheral blood smear contained 20% neutrophil polymorphs, 64% large lymphocytes, and 16% damaged cells. There were only 32,000 platelets in each c.mm of blood (Fig. B). The marrow showed very active erythropoiesis, nearly 40% of the nucleated cells being normoblasts at various stages; many were polychromatic with only partly condensed nuclei. Neutrophil and eosinophil myelocytes were present in fair numbers, but there were few mature granulocytes. Small lymphocytes were normal. There were many large cells with pale nuclei and clear, light-blue cytoplasm. Some of them were primitive cells, with nucleolated nuclei and more basophilic cytoplasm; others had abundant pale cytoplasm and appeared to be a type of monocyte or histiocyte. Phagocytosis was not seen, but occasional cells of this type had vacuolated cytoplasm. They may have been the marrow representatives of the atypical large lymphocytes found in later blood smears and in the smears of siblings. The result of Coombs's test was negative, but platelet agglutinins were demonstrable in the serum (see Table). The blood picture deteriorated. The spleen had been clearly demonstrated as a major site of erythrophagocytosis in previous siblings. In addition, autoantibodies had been detected in Case 2 and possibly in Case 3, and the presence of severe pancytopenia without the usual signs of

FIG. A.—The fourth child.

F. T. G. PRUNTY, R. V. BROOKS, AND D. MATTINGLY: POST-PUBERTAL HIRSUTISM

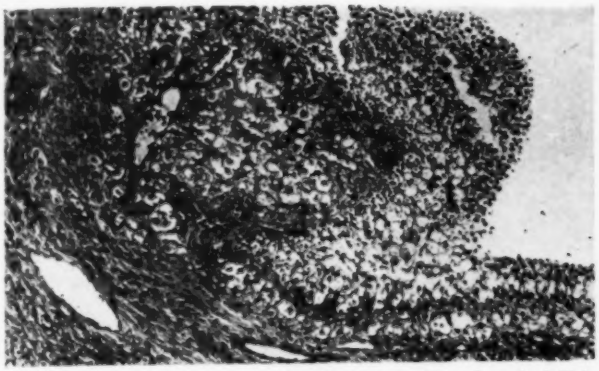


FIG. 1.—Theca proliferation and luteinization at edge of cystic follicle in ovary removed from patient with Stein-Leventhal syndrome. (×96.)

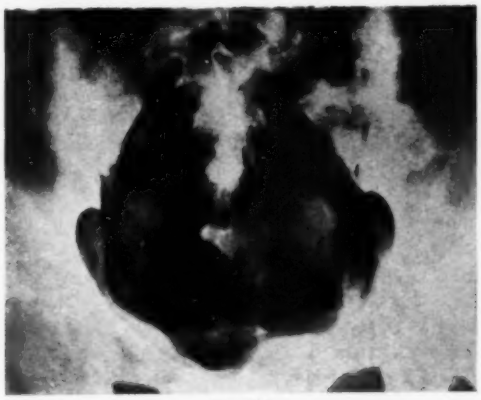
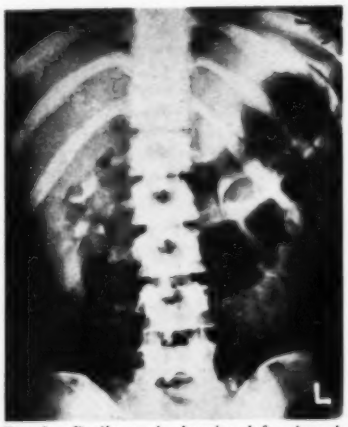


FIG. 2A



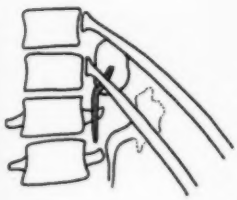


FIG. 3.—Radiograph showing left adrenal cortical tumour with calcified thrombus in left adrenal vein (case in Table VIII). Outline of tumour and thrombus is indicated above renal pelvis in accompanying diagram.

FIG. 2B

FIG. 2.—Radiographs showing ovarian shadows after induction of pneumoperitoneum. A, normal; B, from case of Stein-Leventhal syndrome.

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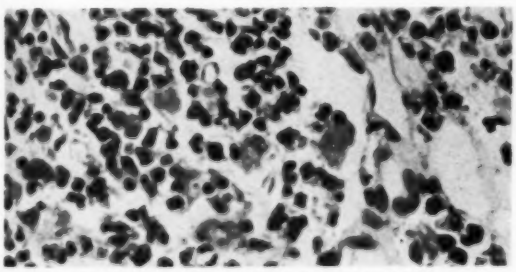

FIG. 1.—Biopsy of spleen showing phagocytes in sinuses containing numerous erythrocytes. (×420.)

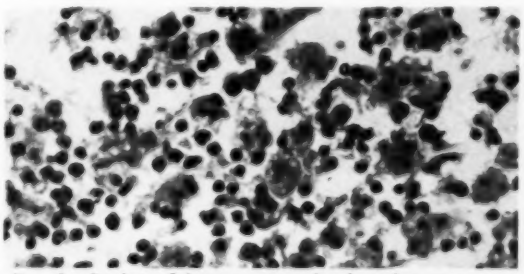

FIG. 2.—Section of bone marrow showing phagocytes containing erythrocytes and occasional nucleated cells. (×420.)

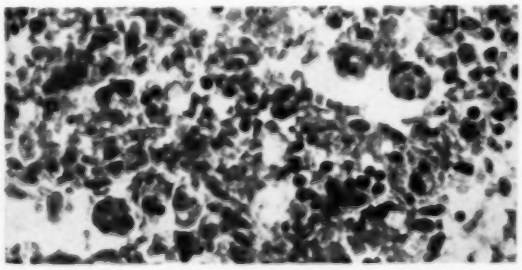

FIG. 3.—Section of lymph node showing phagocytes containing erythrocytes and nucleated cells. (×420.)

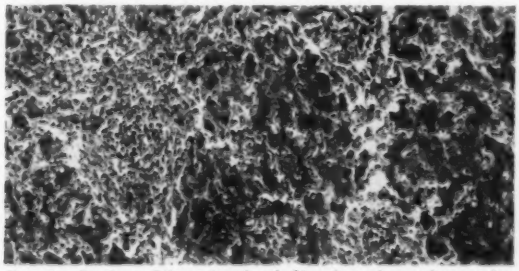

FIG. 4.—Section of liver showing infiltration of portal tracts by histiocytes. (×64.)

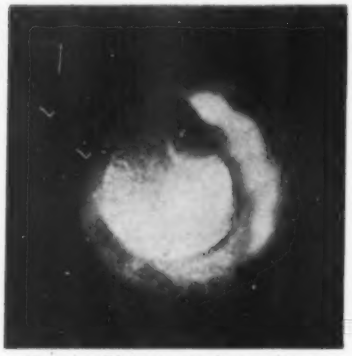

FIG. 1.—Right tympanic membrane.

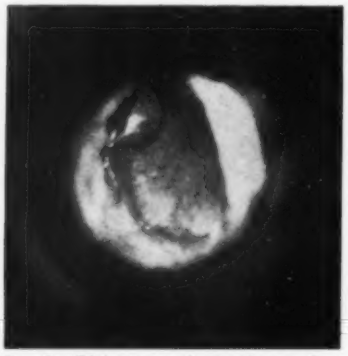

FIG. 2.—Right tympanic membrane after injection of local analgesic.

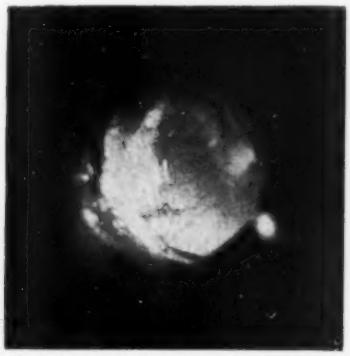

FIG. 3.—Central part of the incision.

FIG. 4.—Entry into tympanic cavity.

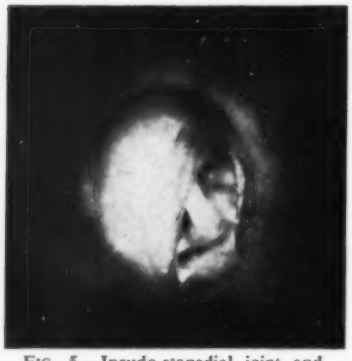

FIG. 5.—Incudo-stapedial joint and stapedius tendon.

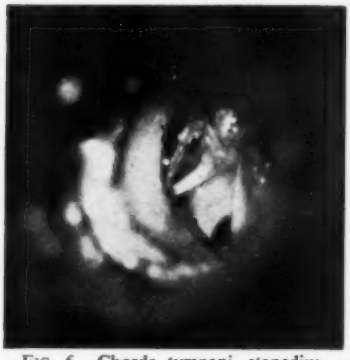

FIG. 6.—Chorda tympani, stapedius tendon, stapes, round-window niche.

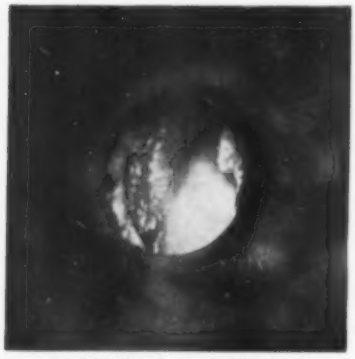

FIG. 7.—Mobilization completed. Tympanic membrane has been replaced.

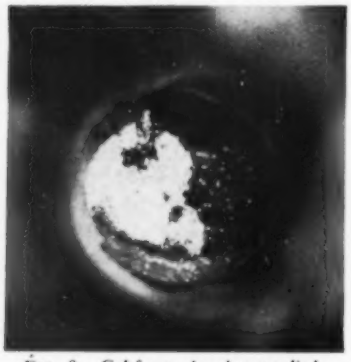

FIG. 8.—Gel-foam dressing applied.

FIG. 9.—A left ear. Seeker is at foot of anterior crus.

FIG. 10.—Showing pool of blood in round-window niche.

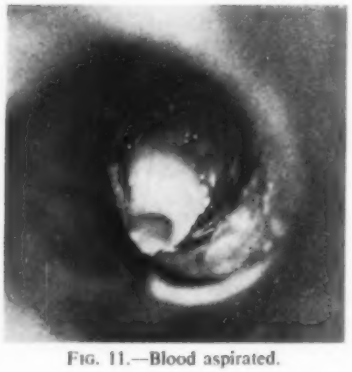

FIG. 11.—Blood aspirated.

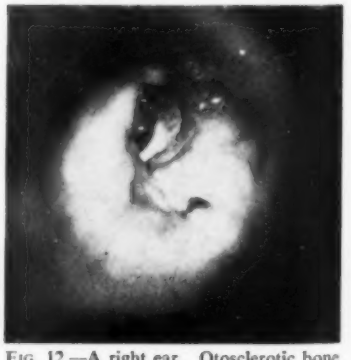

FIG. 12.—A right ear. Otosclerotic bone involving both crura of stapes.

FIG. 1.—Blood film from healthy donor pretreated with normal serum. No nuclear fluorescence.

FIG. 2.—Blood film from same donor as Fig. 1 pretreated with L.E. serum. Nuclear fluorescence present.

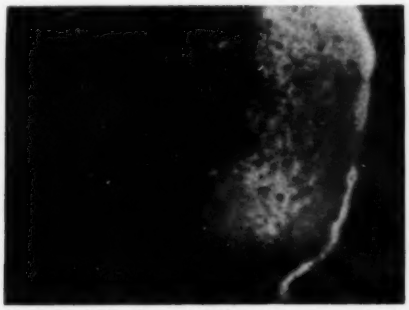

FIG. 3.—Skin from healthy donor pretreated with normal serum. No nuclear fluorescence.

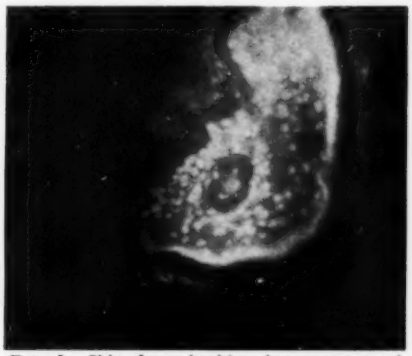

FIG. 5.—Skin from healthy donor pretreated with L.E. serum. Nuclear fluorescence present.

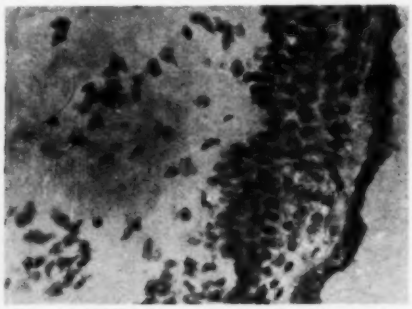

FIG. 4.—Field shown in Fig. 3 stained with Giemsa.

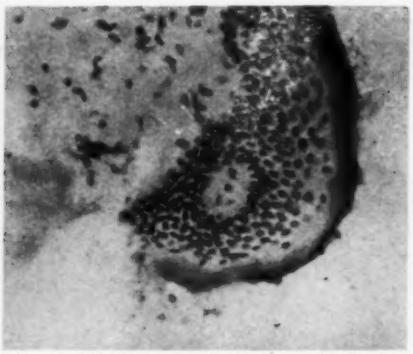

FIG. 6.—Field shown in Fig. 5 stained with Giemsa.

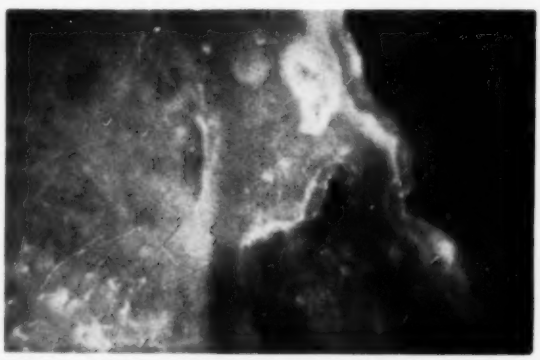

FIG. 7.—Skin from D.L.E. pretreated with autologous serum (Case 7). Diffuse fluorescence in epidermal cells, but nuclei not selectively involved.

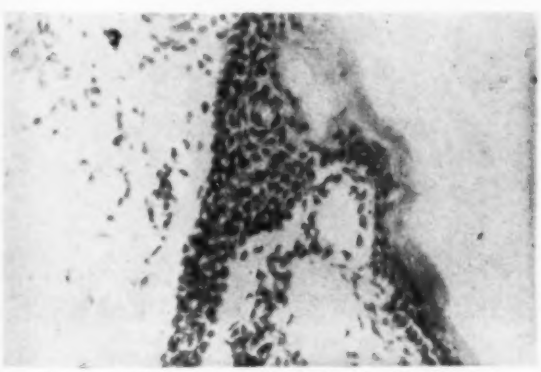

FIG. 8.—Field shown in Fig. 7 stained with Giemsa.

FIG. 9.—Buccal mucosa from healthy individual pretreated with L.E. serum. No nuclear fluorescence. (Brightness of centre of field is due to optical properties of dark-ground condenser.)

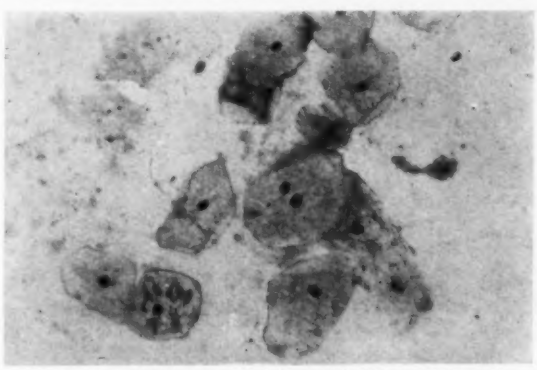

FIG. 10.—Field shown in Fig. 9 stained with Giemsa.

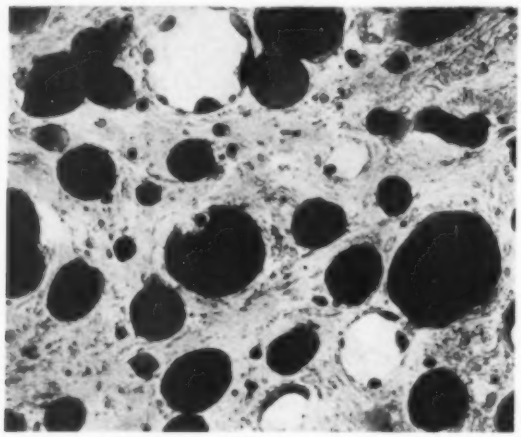

FIG. 1

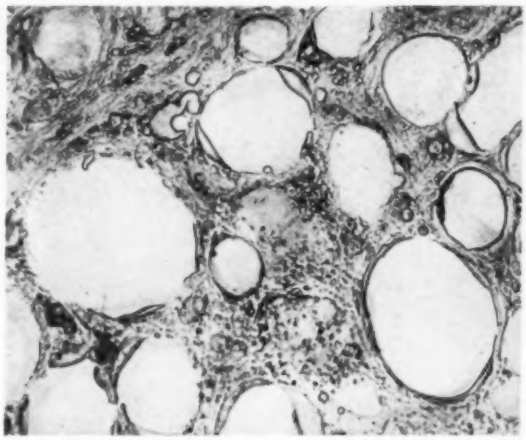

FIG. 2

FIG. 1.—Dense fibrosis of lung with honeycomb of fat-filled spaces, typical of a late stage of oil aspiration pneumonia. (Sudan IV. ×66.)

FIG. 2.—Similar area to Fig. 1 stained with osmic acid and showing no reduction by fat. (×66.)

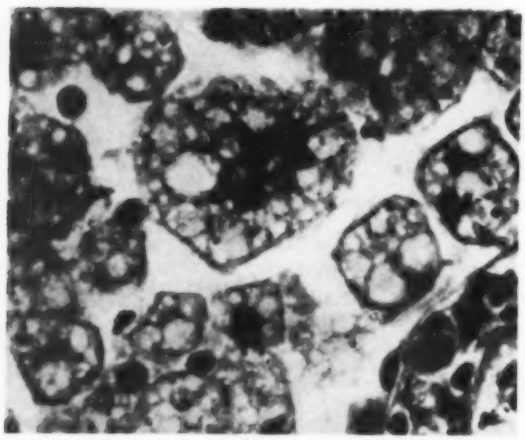

FIG. 3

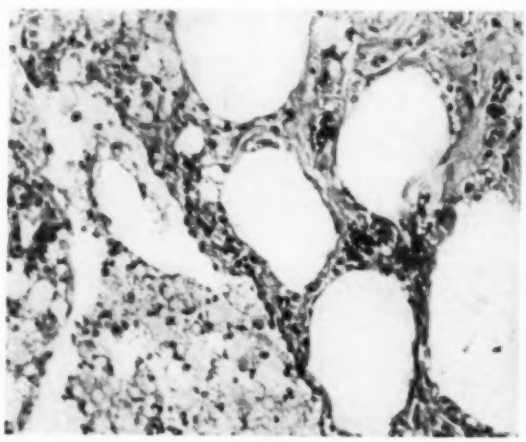

FIG. 4

FIG. 3.—Typical vacuolated lipophages of oil aspiration pneumonia lying in alveolus (H. and E. ×264.)

FIG. 4.—Section of lung showing different stages in reaction to oil. On left are sheets of lipophages between which fibrous strands are beginning to insinuate. Farther to right, fat-filled spaces are enmeshed in fibrous tissue which is cellular in character. Still farther right, fibrous tissue is denser and much less cellular. (H. and E. ×66.)

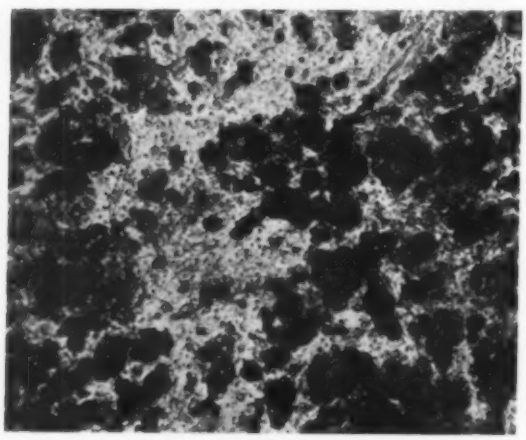

FIG. 5

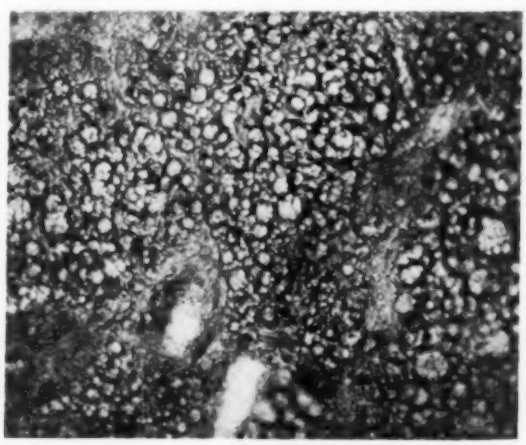

FIG. 6

FIG. 5.—Section of lung showing oil aspiration pneumonia in early stage of development. (Sudan IV. ×66.)

FIG. 6.—Section from same area of lung as Fig. 5 stained with osmic acid. (×66.)

increased blood destruction despite a hyperplastic marrow might have been due in part to hypersplenism. Splenectomy was carried out six days after the patient's admission to hospital. The spleen was enlarged; it measured 10 × 7 × 3.5 cm. and weighed 110 g.; it was of normal consistency and was free from adhesions. The cut surface was deep red and the Malpighian bodies were inconspicuous. On microscopical examination the principal feature was proliferation of endothelial phagocytes in the pulp sinuses and

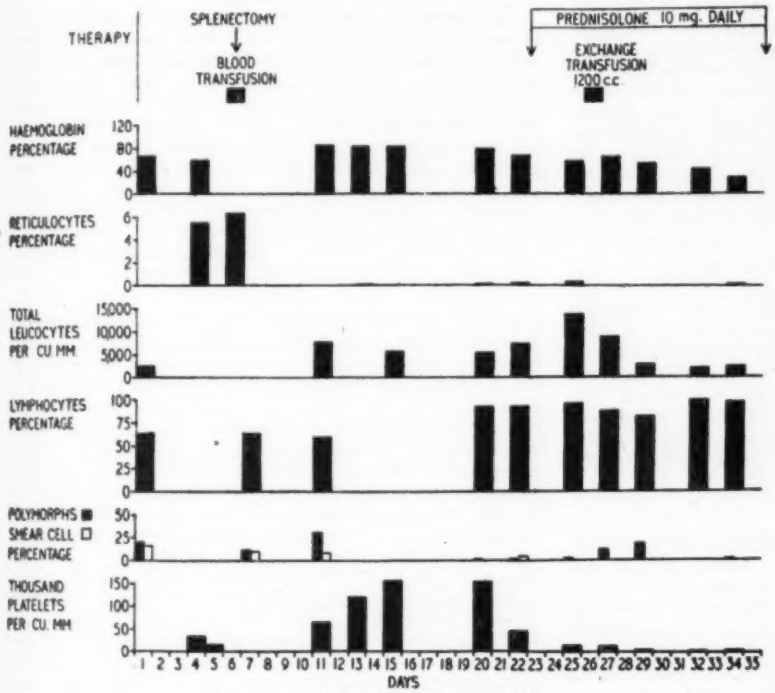

FIG. B.—Progress chart of fourth child.

in smaller numbers in the lymphoid tissue of the Malpighian bodies. The phagocytes were large and most of them had ingested numerous erythrocytes (Fig. B). Some contained ghosts of erythrocytes, or vacuoles only, and some were degenerate and disintegrating. No phagocytosis of nucleated cells was observed. No deposition of haemosiderin was demonstrated. Some Malpighian bodies were small and had almost disappeared; others were of about the usual size but devoid of germinal centres. There was no fibrosis.

The infant's condition improved concurrently with a partial improvement in the blood picture (Special Plate, Fig. 1). Two weeks later, however, deterioration was noticeable. Although corticotrophin had failed to induce a remission in Case 2, a daily dose of 10 mg. of prednisolone was prescribed 15 days after splenectomy, and it was continued without benefit until the baby died.

Two possible explanations existed for the process being re-enacted in the fourth child. Either abnormality of his cells stimulated the proliferation of phagocytes in the reticulo-endothelial system, or the latter was of itself abnormal and engulfed blood cells indiscriminately. The appearance of the red cells was normal. No abnormal haemoglobin was present. It seemed reasonable to expect, however, that if the patient's cells were abnormal their replacement by normal compatible donor cells should be followed by a period of remission. On the other hand, if the patient's cells were normal and the reticulo-endothelial system was abnormal, then compatible donor cells should be removed as quickly as, or even more quickly than, those of the patient. Twenty-six days after admission a 1,200-ml. exchange transfusion was carried out with blood which had been withdrawn within the previous six hours and which had proved compatible with the recipient's blood after most careful cross-matching. At the time of this procedure a sample of the infant's erythrocytes was labelled with radioactive chromium and reinjected with a view to measuring the red-cell survival time.

No improvement followed the exchange transfusion and the child died nine days later. During this period the haemoglobin level fell from 63% to 28%. Seven days after chromium-labelled cells had been injected only 34% of the injected radioactive material was present in the circulation, and at the time of death (that is, Day 9) only 11% remained. It was calculated that 50% of the injected radioactive material had been eliminated in five days. (Mean finding in five normal individuals, 26 days. This is in agreement with the results of Mollison (1956).)

Pathology.—The necropsy was restricted by limitation of the incision to the abdomen. The body was that of a male infant weighing 6,155 g. The skin was moderately jaundiced and there were petechiae on the trunk and limbs. The mucous membranes and nails were pale. The abdomen was greatly distended and a transverse surgical incision on the left side was recently healed. The significant pathological observations were as follows. The liver was moderately enlarged and weighed 447 g. It was light brown, and both the external and the cut surface showed red spots which measured up to 3 mm. in diameter and were slightly depressed. The consistence was normal and no fibrosis was detectable. Lymph nodes were not appreciably enlarged, but many were dull red or purple. The largest were in the upper abdomen. The bone marrow was deep red. Other macroscopical features were those resulting from anaemia.

On microscopical examination the outstanding pathological feature was the presence of many phagocytic histiocytes in various organs. They were conspicuous throughout the reticulo-endothelial system: in the bone marrow, lymph nodes, intestinal tissue, and liver; and also in the interlobular and interacinar stroma of the pancreas and among the disintegrated remains of the foetal cortex of the adrenal glands. The phagocytes were large cells, with swollen, often vacuolated cytoplasm, and in all the situations mentioned many of them contained erythrocytes in numbers varying from one to ten. In the bone marrow (Special Plate, Fig. 2) and lymph nodes (Plate, Fig. 3) nucleated cells had been phagocytosed, but it was uncertain whether these were normoblasts or lymphocytes. The phagocytes lay free in the bone-marrow spaces and in the sinuses of the lymph nodes. In the liver (Plate, Fig. 4) they infiltrated the widened and extended portal tracts and were found also in the sinuses, where they appeared to be proliferated Kupffer cells. This infiltration was not accompanied by any appreciable fibrosis. The depressed red spots noted macroscopically in the liver proved to be areas in which most of the epithelial cells had disappeared, leaving a network of wide sinuses.

In spite of the evidence of active blood destruction by phagocytosis, no deposition of haemosiderin was detected in any situation. The lymphoid tissue in all sites examined showed a reduction in the number of lymphocytes and absence of germinal centres in the follicles.

Further Investigation of Parents (December, 1956—February 1957)

The father and mother were young and apparently healthy. They had not suffered from any significant illnesses earlier in life, but the father had vomited frequently in early infancy. There was no relevant medical history on either side of the family. In neither parent were there any abnormal physical findings, in particular there was no enlargement of liver, spleen, or lymph nodes.

The results of blood examination were as follows. Father: Hb 101%; R.B.C. 4,730,000 per c.mm.; C.I. 1.06; reticulocytes less than 1%. Mother: Hb 100%; R.B.C. 5,890,000 per c.mm.; C.I. 0.84; reticulocytes less than 1%. In films made from the peripheral blood the red cells, white cells, and platelets appeared normal. In both parents there was no increase of red-cell fragility in hypotonic dilutions of saline, the direct Coombs test was negative, the level of bilirubin in the serum was not raised, and there was no excess of urobilinogen in the urine. The father consented to sternal puncture. In smears made from the marrow aspirate the appearances were entirely normal.

The survival time of the parents' own red cells was then measured using radioactive chromium. In the mother 50% of the injected radioactive material had disappeared from the circulation in 27 days, indicating normal red-cell life. The life span of the father's erythrocytes, however, was significantly shortened, 50% of the injected radioactive material being eliminated within 20 days. Subsequently the fate of chromium-labelled cells from a healthy donor was studied, and it was found that their rate of elimination was also more rapid than in normal individuals, the 50% level of radioactivity being reached in 23 days.

Discussion

The apparent homochronous inheritance of a disorder which affected primarily either the blood cells or the reticulo-endothelial system, and which was responsible for the deaths of three siblings (two boys and a girl) and mildly affected the other, may be unique. In each of the fatal cases systemic upset developed in the third or fourth month of life, when each was found to have pancytopenia and enlargement of the liver and spleen. In Cases 2 and 4 the pancytopenia progressed in the presence of an apparently richly reactive, normoblastic bone marrow and in the absence of the usual evidence of haemolysis. Hypersplenism appeared to be a possible explanation of these features, but in the fourth child splenectomy failed to produce a haemopoietic response in keeping with the release of marrow inhibition. A temporary increase in granulocytes and platelets was not sustained. The main cause of the anaemia in each case appeared to be the excessive removal of red cells from the circulation as a result of erythrophagocytosis by histiocytes which had proliferated throughout the reticulo-endothelial system. Leucophagocytosis was also seen. Phagocytosis was never demonstrated in peripheral blood or marrow smears, although a proportion of large, atypical mononuclear cells was seen in both.

That the life span of the red cells was severely shortened was clearly demonstrated in the fourth child. No abnormality in either the appearance of the red cells or their osmotic fragility was found, and the presence of an abnormal haemoglobin was excluded. The occasional detection of autoantibodies in the serum of some members of the family strongly suggested that the excessive destruction of erythrocytes was due not to a red-cell defect but to extracorpuscular factors. Had the last child survived for a longer period, a study of the fate of labelled corpuscles from a healthy donor would probably have confirmed this view, particularly as the haemoglobin level fell with great rapidity after exchange transfusion. Significant observations were, however, made in the father. Although he had at no time any abnormal clinical features, he was shown at one examination to be moderately anaemic, and an autoantibody was found in his serum. At a later date, despite a normal peripheral blood picture, the life span of his own red cells and of donated corpuscles was appreciably shortened, indicating that he was suffering from a haemolytic disorder of extracorpuscular type. It is reasonable to suppose that this was not a coincidence, but that the finding was a milder expression of the fatal illness encountered in three of the children. It would have been of great interest to make a fuller investigation of the surviving child, but red-cell-survival studies were not undertaken because of her age and because the parents had been encouraged to regard her as normal.

The familial incidence of some reticulo-endothelial disorders is well recognized. Thirty-five cases of familial leukaemia have been reported (Wintrobe, 1956). In eight families three or more members have been affected by Hodgkin's disease; it has appeared concurrently in identical twins, and on three occasions affected women have given birth to affected children. Leukaemia has affected as many as five of eight siblings in childhood and six persons in two generations. Wintrobe believes it likely that genetic factors do exert an influence in the aetiology of human leukaemia, but that the mode of inheritance is obscure. The so-called lipoid reticuloses, Gaucher's and Niemann–Pick's disease, are familial, and Letterer–Siwe's disease has been reported in siblings.

The disorder which has been described in this paper presented in a lethal form in three children and as a relatively benign condition in the surviving child and in the father. If the condition was the result of a dominant characteristic, then one clinical picture might have been expected. It seems more likely that the condition was transmitted by a recessive gene, the lethal form being the expression of a homozygous state, and that the surviving child and her father are heterozygotes. Such a difference in the clinical expression of homozygous and heterozygous states is well recognized, as, for example, in thalassaemia, phenylketonuria, and mucoviscidosis, where the heterozygotes may be shown to have a mild haemolytic process, an impaired phenylalanine tolerance, and an increased electrolyte content in sweat, respectively. Investigation of the mother of this family failed to demonstrate any abnormality, but the manifestations of recessive traits in carriers tend to be variable, and the absence of abnormality in the mother is not very unusual. The benign form might be phasic in character, as evidenced by the fluctuation in the condition of the father and of the surviving child. It is possible, therefore, that intermittently repeated examinations of the mother might yet have revealed some abnormality had she not expressed a wish to be excused from further investigation. In a small country community such as that in which the parents were raised the chance of a consanguineous marriage taking place is increased, particularly when the additional complication of illegitimacy is introduced, as in this case. The obtaining of a detailed family pedigree should form an important part of the investigation of further cases.

The disease appears to be a disorder of the reticulo-endothelial system characterized by the widespread proliferation of haemophagocytic histiocytes. The original title of familial haemophagocytic reticulosis appears to be an adequate description.

Summary

The clinical and pathological features of a further case of familial haemophagocytic reticulosis have been described, and an account has been given of investigations into the aetiology. The possible mode of inheritance is briefly discussed.

We are indebted to Professor R. W. B. Ellis for his helpful criticism of this paper, to Professor J. H. P. Jonxis, of Groningen, for the haemoglobin type of the fourth child, and to Dr. R. A. Cumming for the results of serological tests.

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REACTION OF LUPUS ERYTHEMATOSUS SERUM WITH NUCLEI OF CIRCULATING AND NON-CIRCULATING CELLS

BY

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[WITH SPECIAL PLATE]

Friou (1957) was the first to demonstrate that tissue cells brought in contact with serum from patients suffering from disseminated lupus erythematosus (D.L.E.) and exposed subsequently to fluorescein-conjugated anti-human-globulin (A.H.G.) serum showed specific nuclear fluorescence. This application of Coons's fluorescent antibody technique has been further studied by Friou, Finch, and Detre (1957, 1958) and by Holborow *et al.* (1957). In addition, it has been demonstrated by Mellors *et al.* (1957) and Holman and Kunkel (1957) that the inclusion bodies in L.E. cells fluoresce on exposure to fluorescein-conjugated A.H.G. serum.

These results provide strong evidence for the belief that the serum in D.L.E. contains a globulin with an affinity for the nuclei of tissues and leucocytes. It has been suggested that this globulin is identical with the factor responsible for the formation of L.E. cells. Friou (1958) has shown that the capacity of serum from cases of D.L.E. to induce both phenomena is abolished by absorption of the serum with nucleohistone.

In the studies referred to attention has been mainly directed to the reaction of D.L.E. serum with tissues derived from other sources than patients with D.L.E. With the exception of reports on fluorescence of L.E. cells exposed to fluorescein-conjugated A.H.G. serum, no comment on the effect of D.L.E. serum on D.L.E. tissue has been found in the literature. It seemed important to determine whether D.L.E. tissue differed from normal tissue on exposure to D.L.E. serum, and in this report the results of such a study are presented.

Materials

Human Sera.—Serum was obtained from eight patients suffering from D.L.E. In all cases L.E. cells had been found on more than one occasion. All patients but one (Case 3) were receiving prednisolone or cortisone at the time of investigation, the daily dose being shown in the Table. Control sera were obtained from healthy members of the hospital staff. Sera were not heated before use, and when necessary were stored at −15° C. In a preliminary experiment it was found that sera retained their reactivity on storage for periods of at least six weeks.

Leucocytes.—Blood was obtained by ear-prick, films being spread on microscope slides as for routine haematological examination. Films were not fixed, and were used on the day of preparation.

Skin.—Portions of skin were obtained by biopsy from two patients (Cases 4 and 7) and from two healthy donors of corresponding blood groups. One patient (Case 4) and one control were of blood group O, and all sera were tested on sections from these individuals. Within one minute of biopsy the skin was frozen in test-tubes dipped in solid CO_2–acetone mixture. Sections were cut at 4–6 μ in a cryostat at −20° C. The sections were then transferred to slides, thawed, dried by fan, and used on the day of biopsy.

Buccal Mucosa.—Squamous epithelium was obtained by gently scraping the buccal mucous membrane with a metal spatula. The scrapings were transferred to slides and allowed to dry at room temperature. As with blood films and tissue, the cells were examined on the day of preparation.

Fluorescein-conjugated Anti-human-globulin. — Commercial A.H.G. (Coombs's) serum was conjugated with fluorescein isocyanate by the method of Coons and Kaplan (1950). The conjugated serum was absorbed with sheep-liver powder to reduce non-specific precipitation in tissues.

Methods

Sections of tissue or preparations of cells were exposed to human serum in a moist atmosphere at 37° C. Except when otherwise stated, the time of incubation was 30 minutes and the sera were undiluted. The preparations were then washed in two changes of phosphate-saline buffer at *p*H 7.0 and covered with a few drops of undiluted fluorescein-conjugated A.H.G. serum. After 30 minutes at room temperature the preparations were again washed in buffered saline and mounted in buffered glycerol at *p*H 7.0. Cover slips cut from OY12 (ultraviolet-absorbing) glass were used.

The specimens were examined in the fluorescence microscope as described by Alexander (1958), with the exception that plain glass microscope slides were used in the present work. When required the preparations were photographed and the field plotted with the aid of the graduated mechanical stage of the microscope. The cover slips were floated off and the tissue fixed in undiluted methyl alcohol. The preparations were then stained with Giemsa's stain and mounted in balsam. Fields were identified and rephotographed using a source of visible light.

Results

In most experiments the presence or absence of nuclear fluorescence was readily recognized, and examples are shown in Figs. 1, 2, 3, and 5 on the Special Plate. Figs. 4 and 6, which correspond to Figs. 3 and 5 respectively, are included as an aid to identification of individual nuclei.

Nuclear fluorescence as seen in Figs. 2 and 5 was observed only in tissues or cells which were pretreated with L.E. serum. Pretreatment with serum from healthy individuals or the direct application of fluorescein-conjugated A.H.G. serum to the preparations invariably gave negative results.

Table Showing Nuclear Fluorescence in Tissues and Cells Pretreated with Sera from D.L.E.

Serum from Case No.	Reaction of Serum with				Daily Dose of Steroid (P=Prednisolone) (C=Cortisone) (mg.)
	Autologous Leucocytes	Group O Leucocytes (Healthy Donor)	Skin from D.L.E. (Group O)	Skin from Healthy Group O Individual	
1	−	+	−	+	62·5 (C)
2	−	+	−	−	5·0 (P)
3	+	+	−	+	—
4	+	+	+	+	15·0 (P)
5	+	+	−	−	5·0 (P)
6	+	+	+	+	50·0 (C)
7	+	+	+	+	5·0 (P)
8	+	+	−	+	30·0 (P)

+ = Nuclear fluorescence present. − = Nuclear fluorescence absent.

The sera from eight patients suffering from D.L.E. were applied to autologous blood films, blood films from healthy donors, sections of skin from a patient with D.L.E., and sections of skin from a healthy individual. All but the autologous cells were obtained from individuals of blood group O. The results of this experiment are shown in the Table. Leucocytes from the healthy subject pretreated with all sera tested showed nuclear fluorescence when subsequently exposed to fluorescein-conjugated A.H.G. serum. Nuclei of autologous leucocytes fluoresced on pretreatment with six of the eight sera. Nuclei in sections of skin from a healthy subject

fluoresced when pretreated with six of eight sera, but nuclei in skin from a patient with D.L.E. (Case 4) showed fluorescence when pretreated with only three of the eight sera.

In view of the apparent diminution of affinity of L.E. serum for nuclei in L.E. tissue, skin obtained from another patient (Case 7) was examined. Pretreatment of this material with autologous serum gave an equivocal result, as shown in Fig. 7 on the Special Plate. Although diffuse fluorescence of epidermal cells was seen, selective fluorescence of nuclei did not occur. This finding cannot be explained by failure of autologous tissue and serum to react, as nuclear fluorescence was observed when tissue from Case 4 was pretreated with autologous serum. It was established by two experiments that the serum from Case 7 had not lost its potency. The serum was used to pretreat leucocytes from a healthy individual, and nuclear fluorescence was observed when the serum was diluted to 1:4,000. Undiluted serum produced nuclear fluorescence when applied to the cells for one minute.

The necessity for using fresh material in this type of investigation has been stressed by Holborow *et al.* (1957). The difficulty of obtaining regular supplies of tissue by biopsy is considerable, and it was decided to examine cells obtained by scraping the buccal mucosa. These could be taken as representative of fixed tissue cells as distinct from the circulating leucocytes. However, the nuclei of squamous cells from healthy individuals or patients with D.L.E. exposed to D.L.E. serum failed to show fluorescence on subsequent treatment with fluorescein-conjugated A.H.G. serum (Special Plate, Figs. 9 and 10). When, however, the time of exposure to D.L.E. serum was extended to 1½ hours nuclear fluorescence was observed in cells which had disrupted. As there was also evidence of diffuse bright fluorescence in structures thought to be of cytoplasmic origin, no conclusion can be drawn from these experiments. Further investigation with specific counter-stains for nuclear material is planned.

Discussion

These results confirm the findings of other workers that the nuclei of cells exposed to serum from patients suffering from D.L.E. adsorb a globulin detectable by application of fluorescein-conjugated A.H.G. serum. This property of L.E. serum is not apparently influenced by administration of steroid hormones.

It has been shown that the phenomenon is readily demonstrable in unfixed blood films. This technique, which avoids the need for preparing films from "buffy coats," would be useful in any large-scale investigation of the phenomenon in other diseases.

The observation that nuclear fluorescence is not present in tissue from cases of D.L.E. exposed directly to fluorescent A.H.G. serum is in agreement with the findings of Mellors *et al.* (1957) in the D.L.E. kidney, and supports the hypothesis that absorption of L.E. globulin on nuclei occurs only *in vitro*. The fact that tissues and leucocytes derived from patients with D.L.E. appear to be less susceptible to uptake of globulin from L.E. serum may be explained by the relatively small number of patients available for study, but the anomalous behaviour of the serum from Case 7 toward nuclei in autologous skin and the nuclei in the skin of another patient is of interest. Recent experiments, which are still incomplete, suggest that the time of incubation of tissue and L.E. serum may have a considerable influence on the intensity of nuclear fluorescence and that individual sera and tissues may differ appreciably in the rate of reaction.

The results of experiments with squamous epithelium suggest that intact tissue cells resist invasion of the specific globulin in L.E. serum. It has been noted in examination of thick sections of skin that nuclear fluorescence may be apparent in the superficial layer, but not in deeper layers. Leucocytes, however, seem to be extremely susceptible to the specific globulin in L.E. serum, and this susceptibility may well be associated with their natural property of phagocytosis.

Summary

With the use of Coons's fluorescent antibody technique it has been confirmed that sera from patients suffering from D.L.E. contain a globulin which combines with nuclei of tissue cells and leucocytes. In a study of sera from eight cases of D.L.E. it was observed that nuclei of leucocytes from healthy individuals showed the greatest affinity for the specific globulin. No evidence of uptake of globulin in tissue from D.L.E. was found *in vivo*, but *in vitro* such tissue had less affinity for the specific globulin than tissue from healthy subjects. Nuclei of intact squamous epithelial cells pretreated with D.L.E. serum did not fluoresce on exposure to fluorescein-conjugated anti-human-globulin serum.

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LIQUID PARAFFIN AS A CAUSE OF OIL ASPIRATION PNEUMONIA

BY

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[WITH SPECIAL PLATE]

Liquid paraffin has, for various reasons, been under suspicion at different times since it began to be used to any extent medicinally at the beginning of this century. It has been charged with preventing intestinal absorption of food in general, and of vitamin A and its precursor, carotene, in particular, and on this latter count there is some justification for the charge. Since liquid paraffin is a mixture of liquid hydrocarbons obtained from petroleum, the possibility that it might contain carcinogenic fractions has been investigated (Boyd and Doll, 1954). At one time there was a practice of instilling liquid paraffin into the peritoneal cavity with the avowed object of preventing adhesions. The result has been to produce, in a number of cases, an oil granuloma of the peritoneum (Bennett and Collins, 1952). Probably, however, the most common danger arising from the medicinal use of liquid paraffin is the production of oil aspiration pneumonia.

The pneumonia which results from aspiration of oils and fats has been dealt with extensively in American literature, but has not received the same attention in Britain, although its incidence in this country may not be any less. The diagnosis of the condition in life is not

easy, since similar lesions may be produced by other agencies, and fats and oils are not often considered as aetiological agents, because of a fairly general lack of awareness of their ability to produce such lesions and a failure to elicit, in consequence, the relevant facts in the patient's history. In the cases described in this paper aspiration of oil was not considered in diagnosis during life. The diagnosis at necropsy also presents some difficulty.

Classification and Predisposing Factors

Ikeda (1937) classified oil aspiration pneumonia into two types, which he called "adult" and "infantile." The "infantile" type occurs in debilitated children and adults as a result of the administration of food and drugs containing animal oils. This type is essentially a diffuse low-grade pneumonia, and one of the main grounds of distinction from the "adult" type is that it may undergo resolution. The "adult" type occurs only among the older age groups as a result of habitual self-administration of liquid paraffin, either orally or intranasally, in large total amounts. Animal oil is of little importance in the "adult" type, where the lesion is a chronic granuloma.

Among the factors predisposing to aspiration of oil into the lungs are the feebleness associated with early infancy and old age, the disabilities arising from affections of the central nervous system, debility, recumbency, dysphagia, and lesions of the mouth, throat, oesophagus, and upper respiratory tract. The character of the oil also is an important factor. Liquid paraffin is implicated as the causal agent in the great majority of cases. Its blandness would seem to be the reason for its known capacity to enter the bronchial tree without exciting any reflex action. The type of case in which oil aspiration pneumonia is most likely to be found is the chronic sufferer from respiratory infection who for long periods uses oral or nasal sprays of which liquid paraffin is an ingredient, or the sufferer from chronic constipation who seeks relief in a regular oral dose of liquid paraffin over long periods (Freiman *et al.*, 1940).

Pathological Changes

There cannot be said to be a typical naked-eye appearance. There are irregular areas of consolidation in the lung, varying in size from 1 cm. or less in diameter to that of a whole lung segment. The lesions, being fibrous, have a tough or hard consistence, and are grey or yellow in colour. On naked-eye examination and radiologically (Siddons, 1958) they have been most often wrongly diagnosed as neoplastic infiltration or as caseous consolidation of tuberculosis. Microscopically, different fields may show different stages of reaction. In some areas an accumulation of phagocytes may be found occupying the alveoli. They are large, foamy, and vacuolated in varying degree. Strands of collagen fibres may be seen insinuating between these lipophages. Giant cells formed by the coalescence of the lipophages are commonly present. In yet other areas there is dense fibrosis with circular lacunae. Appropriate stains show these lacunae to be filled with fat.

As might be expected, there are a number of complications which will each add its quota to the appearances described. Recurrent bronchopneumonia, bronchiectasis, abscess formation, and empyema have been known to complicate the disease. Bronchogenic carcinoma has been suggested as a complication.

The crux of the diagnosis lies in the demonstration of fatty material in lacunae in the densely fibroid lung tissue. To distinguish between mineral oils on the one hand, and vegetable and animal oils on the other, use has been made of the reaction of osmium tetroxide, which is reduced by the animal and vegetable oils to give a black precipitate, whilst mineral oils have no such action. Some investigators have carried out chemical analysis of lung tissue (Jampolis *et al.*, 1953; Wagner *et al.*, 1955).

Case Histories

Case 1.—A woman aged 54 was admitted to hospital on January 17, 1956, with a diagnosis of bronchitis, bronchiectasis, and right-sided heart failure. There was a history of chronic cough since childhood. A radiological report at that time mentioned gross bilateral emphysema secondary to chronic bronchitis, with bilateral bronchiectasis in the lower lobes. Investigation for tuberculosis was negative.

On admission she had marked dyspnoea at rest. There were diffuse bronchospasm and expiratory and inspiratory rhonchi, with coarse crepitations at both lung bases. Jugular venous pressure was raised. There was oedema of the ankles and sacrum. Laboratory investigation of the sputum showed normal flora, and two specimens were negative for acid-fast bacilli. The urine was sterile on culture, and apart from a trace of albumin was not otherwise abnormal. Blood urea was 47 mg. per 100 ml. Haemoglobin 87% (Haldane). White cells numbered 10.400 per c.mm., with normal differential count. Chest *x*-ray report on January 26 was a repeat of previous findings, but in addition there was general enlargement of the heart, the appearances suggesting myocardial failure. The patient responded temporarily to treatment, but died on February 7, 1956.

At necropsy the main findings were as follows. The abdomen was distended and the ankles and legs were oedematous. The trachea and bronchi were filled with frothy mucus. Both lungs showed diffuse emphysema, with extensive areas of patchy consolidation, particularly in the lower lobes. There was marked prominence of the bronchi and bronchioles. The right ventricle was hypertrophied. The liver on cut surface showed a nutmeg pattern. The peritoneal cavity contained 2 pints (1.1 litres) of serous fluid.

Histological examination of the lungs showed the changes of chronic bronchitis and emphysema. In many areas the alveoli were filled with large, foamy, pink macrophages, many of which contained two or more nuclei. In other areas there was a picture of extreme disorganization characterized by the presence of giant cells of bizarre shape, suggestive of foreign material in the lung tissue. In yet other areas were large collections of lymphocytes and plasma cells. There were also extensive areas of fibrosis, in the meshes of which, on staining with Sudan IV, were revealed a number of oil globules of varying size. These globules were found not to reduce osmium tetroxide. It was therefore concluded that the findings disclosed the presence of an oil aspiration pneumonia, in both acute and chronic stages, due to liquid paraffin.

Subsequent inquiry yielded no information as to the source of the aspirated oil. It was surmised that it was probably an oral or nasal spray containing liquid paraffin.

*Case 2.**—A man aged 55 years, a universal grinder in a steel foundry, died suddenly on November 1, 1957. For several years he had been under the care of his doctor on and off because of pains in the chest, shortness of breath, and chronic cough; he had, in fact, been treated for bronchitis. Three weeks before his death he was seen by his doctor because of an attack of "influenza," and he had never fully recovered.

The main findings at necropsy related to the chest. There was a quantity of mucopus in the trachea. In the lower lobe of the left lung were two dense fibrous masses, each about 1 in. (2.5 cm.) across. A similar mass was present just above the hilum of the right lung. There was no significant emphysema. The heart was substantially dilated and hypertrophied on the right side. Pulmonary fibrosis was present, and an important point was whether it was of industrial or non-industrial origin.

Histological examination revealed varying degrees of fibrosis throughout the lungs. In many areas the appearance was of a honeycomb of clear spaces, which by staining with Sudan IV were shown to be filled with fat (Special Plate,

*This and the following cases were the subject of necropsies undertaken on behalf of H.M. Coroners for the City of Sheffield and the County Borough of Rotherham.

Fig. 1). Osmium tetroxide was not reduced by this fat (Special Plate, Fig. 2). The framework of the honeycomb was of fibrous tissue, but this varied in appearance from area to area. In some areas this framework was of wide, dense, relatively acellular fibrous tissue, and here the clear spaces were largest in diameter. In other areas the fat-filled spaces were smaller and the fibrous-tissue framework was more slender and relatively cellular, the cells being a mixture of fibroblasts and vacuolated macrophages, also shown to be filled with fat. Occasional giant cells were to be seen in this fibrous framework. In some areas the normal alveolar pattern was to be seen, many of the alveoli containing numbers of the large macrophages in various stages of vacuolation, which we have learned to associate with lipoid pneumonia (Special Plate, Fig. 3). Here and there throughout the lung fields were collections of lymphocytes and plasma cells. The basement membrane of the bronchi was thickened. No evidence of silicosis or tuberculosis was noted. There was dramatic narrowing of the branches of the pulmonary artery, with marked medial thickening. This was seen to a lesser extent in areas of lung tissue only slightly affected by fibrosis.

The cause of death was cor pulmonale due to pulmonary fibrosis following lipoid pneumonia. In view of the findings an effort was made to trace the source of the aspirated oil, and it was found that the deceased had been in the habit of taking liquid paraffin as a purgative. This was the only ascertained source from which the lesion could have arisen.

Case 3.—A man aged 78 who had worked in various coalmines all his life. Since the age of 70 he had had at least two strokes, from which he had made substantial recovery. For a number of years he had had shortness of breath, cough, and chest pains. By July, 1957, when he was admitted to hospital for a minor condition, he could do little more than totter about owing to senility. He was kept in hospital because of the difficulty of home nursing, and during his stay a chest radiograph was reported as showing nodular opacities in both lungs due to pneumoconiosis. On December 11, 1957, while sitting in the ward, he had sudden pain in the left leg, and examination elicited all the signs of arterial blockage in this limb. Gangrene of the limb developed, and he died on December 13.

Necropsy was undertaken to determine whether pneumoconiosis was the cause, or a contributory factor in the cause, of death. He was found to have died of bronchopneumonia due to gangrene of the left leg caused by femoral-artery occlusion and arteriosclerosis. An incidental finding was that in the lower part of the middle lobe of the right lung there was a fibrous honeycombed area, which was not pigmented and the appearance of which suggested that it might be an oil granuloma. Histological examination of this area showed that three stages of reaction could be distinguished (Special Plate, Fig. 4). In some fields the alveolar septa could be made out, and within the alveoli were collections of cells showing various degrees of vacuolation, most of them being, in fact, of signet-ring shape. Sudan-IV staining revealed them to be filled with fat. Their nuclei and cell membranes were in various stages of disintegration. Fine fibrous strands were just beginning to make their appearance, insinuating amongst these lipophages. In other fields the alveolar pattern was obliterated, and there were sheets of these signet-ring cells, distended in varying degree with fat, interspersed here and there with not very large clear spaces, which also proved to be filled with fat. In this type of field fibrous bands were more obvious and giant cells were also present. In yet other fields the picture was of a honeycomb of large clear spaces of varying size, shown to be filled with fat. Osmium tetroxide was not reduced by this fat. The framework of the honeycomb was dense fibrous tissue.

So far as the relatives knew, he had not been in the habit of taking liquid paraffin. He was described, however, as being always constipated and taking remedies for that condition. It may therefore very well be that he was in the habit of taking liquid paraffin unknown to his relatives.

Case 4.—A widower aged 79, retired pattern-maker, died suddenly on February 14, 1958. He had for some time been in failing health, and had been under the care of his doctor in the recent past, having had two attacks diagnosed as cerebral thrombosis, but at the time of his death had not been seen by his doctor for some weeks.

At necropsy he was found to have generalized arteriosclerosis, with two areas of old softening in the left cerebral hemisphere. The lungs showed bronchopneumonic change, and indeed the cause of death was bronchopneumonia complicating arteriosclerosis and cerebral thrombosis. In the lower lobe of the right lung a patch of consolidation was discovered, which was larger and had a much harder consistency than the surrounding patches of bronchopneumonic consolidation. Histological examination of this area revealed a picture similar in essentials to that described in Case 3. Sudan-IV staining showed the area to contain a large amount of fat (Special Plate, Fig. 5), which failed to reduce osmium tetroxide (Plate, Fig. 6).

Discussion

For practical purposes the agent responsible for oil aspiration pneumonia in adults is liquid paraffin. It gains access to the lungs most easily by its use as an ingredient of nasal or oral sprays. Some years ago it was commonly found in such sprays, and we cannot but feel that there must exist a considerable number of oil granulomata of the lung arising from their use. The evidence suggests that, once in the lung, liquid paraffin remains as an inert foreign body for many years, and probably permanently. From inquiries we have made it appears that the tendency now is for nose drops and sprays to be made up in an aqueous medium. A substantial proportion (about 20%) is, however, still being manufactured in a medium containing liquid paraffin, and we feel that their manufacture in an oily medium should be stopped. It is also clear that liquid paraffin gains access to the lungs as a result of oral administration, even in those who suffer no disability. A bland oil introduced by catheter into the pharynx of a healthy adult whilst asleep on his back was shown to be present in the lung the following morning (Pirie, 1932). It appears that there is still in Great Britain a steady sale for liquid paraffin as a laxative, and in our opinion its use for this purpose requires reappraisal.

Oil granuloma of the lung is largely preventable. Its presence is known to dispose to recurrent respiratory infection, and in these days when our lungs have to contend with so many other noxious substances this is one lesion which, however small, we can well afford to be without.

Summary

Four cases of oil aspiration pneumonia are described, two in which it was a contributory cause of death and two in which it was an incidental finding.

The pathogenesis and pathology of the condition are discussed.

The use of liquid paraffin as an ingredient of nasal and oral sprays, and also as a laxative, is criticized.

Our thanks are due to Dr. C. H. Hollins and Dr. T. V. Cooper, of Dorchester, for their assistance and for permission to publish the clinical details of Case 1. We are also grateful to A. P. Lockwood, Esq., H.M. Coroner for the City of Sheffield and for the Rotherham Division of the West Riding of Yorkshire, for permission to publish details of Cases 2 and 4; and to N. S. Robson, Esq., H.M. Coroner for the County Borough of Rotherham, with whose authority we publish details of Case 3. For technical assistance and the preparation of the illustrations we are indebted to Mr. S. J. Gray.

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DISPENSABILITY OF POST-OPERATIVE PENICILLIN IN SEPTIC-HAND SURGERY

BY

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The aim of this work was to evaluate the common use of penicillin after operations upon septic lesions of the hand. Localized infections only were considered, and attention was focused principally upon the rate of healing of abscess cavities following the evacuation of pent-up pus. Patients were treated in a special clinic, for Webster (1947) and other workers have obtained improved results by centralizing the treatment of hand sepsis.

Wilkes (1954) emphasized the economic importance of sepsis with a large series of hand infections where the average time lost from work was 24 days. A Ministry of Pensions and National Insurance digest for 1953–4 shows that the number of spells of certified incapacity due to cellulitis and abscess was 6% of the total from all causes. Although falling, this figure leaves no room for complacency, and close inspection of the methods of dealing with this type of lesion, with revision of these therapies where necessary, is constantly indicated.

Scope of the Investigation

All patients required surgery and were treated as out-patients. Children under 10 years were excluded. Each patient was assigned without bias to one of three categories —those dealt with by surgery alone, by surgery plus oral penicillin, or by surgery plus depot penicillin. There were 42, 34, and 27 patients respectively in each of these categories who had received various forms of chemotherapy elsewhere before attending the hand clinic.

The diagnostic classes were: (1) *Paronychia* of any degree, except with pus deep to the nail. (2) *Onychia:* pus under the nail (*a*) tracking from an adjacent focus such as a terminal abscess or paronychia, or (*b*) developing *in situ*—for example, an infected subungual haematoma. (3) *Pulp abscess* of the terminal pulp of the finger. (4) *Other abscesses:* (*a*) subcutaneous, on the volar or lateral aspects of a finger; (*b*) dorsal abscess of the hand or finger, often originating in an infected hair follicle; (*c*) web abscess; (*d*) palmar space abscess. (5) *Septic blister:* occasionally rectified if a subcutaneous extension was found at operation. (6) *Chronic infections* were those whose pre-operative duration exceeded 27 days.

When clinically indicated radiographs (of both hands) were taken.

At operation swabs were taken from the exposed infected tissues for culture and for sensitivity tests to penicillin and erythromycin.

The criteria of healing were a dry completely epithelized wound, full function of the affected member, and no need for further dressings or attendance. The healing-time was the number of days between operation and final discharge.

All the patients were seen by me pre- and post-operatively; some of the operations were done by colleagues with agreed uniformity of procedure.

Surgical Technique and Post-operative Treatment

Each loculus of pus and the point of maximal tenderness were ascertained with patience and precision in the pre-operative planning of an approach to the lesion. The fore-limb was thoroughly washed and upper garments were removed. All operations were performed under general anaesthesia (trichlorethylene, nitrous oxide, and oxygen) in a bloodless field obtained by elevation of the limb and applying a pneumatic tourniquet.

The planned incision, remote from pressure areas, of minimal length, and in the optimum position for drainage, was generally made in the line of a skin furrow (longitudinal or slightly oblique on the antero-lateral aspect of a finger or transverse on the dorsum). Sometimes an undesirable site where the abscess pointed had to be used.

The roof of a septic blister was removed and a collar-stud extension sought. In paronychia a formal flap was raised and an appropriate portion of the nail-base removed; a unilateral incision sufficed for less extensive cases. For onychia, only nail undermined by pus was removed; this was occasionally combined with a unilateral paronychia incision or the opening of a terminal abscess. Web-space abscess was opened by an antero-posterior incision.

Pus and slough were removed by gentle mopping or excision and the abscess cavity was inspected by direct vision. Loculations were opened, avoiding unnecessary interference with healthy tissue. The skin edges, always in a precarious state of vitality, were never forcibly retracted or held by coarse instruments. Only the corner of a small portion of tulle gras was slipped between the lips of the incision or under the paronychia flap. Early in the investigation it seemed beneficial to avoid too much tulle gras, so just enough was used to keep the wound edges apart or to cover a raw area with a little circumferential overlap.

A generous dressing of gauze and cotton-wool was firmly applied, the tourniquet released, and the limb elevated during the recovery period. The arm was kept in a sling and daily exercise periods were advised. Codeine compound tablets were prescribed. Two days after operation a simple dry dressing was applied, and also at later inspections at two- or three-day intervals, an infrequency which reduced the chance of cross-infection, the expenditure of materials, and the strain on the dressings staff.

Oral penicillin was given at the makers' recommendation of 1,200,000 units of "crystapen" daily in divided doses. A printed dosage schedule was included with each supply of tablets and a few patients suspected of not adhering to it were excluded from the series irrespective of their clinical progress.

Depot penicillin was given by intramuscular injection as "seclopen," 1 ml. containing 300,000 units of procaine benzylpenicillin and 100,000 units of sodium benzylpenicillin, morning and evening until the inflammatory reaction had subsided and the wound was virtually healed. Serum levels of penicillin were estimated in each of three blood samples obtained by venepuncture on successive post-operative days before the morning injection in 42 patients of this group.

Results

Of the 357 patients treated, 16 (4.4%) failed to return for dressings, 15 (4.3%) had chronic infections, and 6 (1.7%) had complications. No case of erysipeloid was seen. A patient with acute suppurative tenosynovitis and another two with septic interphalangeal arthritis were referred for in-patient treatment. Both cases of palmar abscess were superficial to the aponeurosis.

Table I shows that in the "depot penicillin" treatment group the overall average healing-time was 0.23 day less than in the "no chemotherapy" group. Shortening of the average healing-times in the depot category for onychia, pulp abscess, other abscesses, and septic blister was 0.2, 1.0, 0.4, and 0.6 day, respectively; paronychia took 0.02 day longer. In the "oral penicillin" category the healing-times were shorter in onychia, pulp abscess, and other abscesses by 2.1, 1.2, and 0.4 days respectively, but in the paronychia group healing took 1.6 days longer.

TABLE I.—*Results of Treatment*

Type of Lesion	No Chemotherapy		Oral Penicillin		Depot Penicillin		Total No. of Patients	Average Healing-time (Days)
	No. of Patients	Average Healing-time (Days)	No. of Patients	Average Healing-time (Days)	No. of Patients	Average Healing-time (Days)		
Paronychia ..	39	8·46	34	10·06	29	8·48	102	9·00
Onychia ..	13	8·92	10	6·80	8	8·75	31	8·19
Pulp abscess ..	20	11·10	31	9·90	31	10·13	82	10·28
Other abscesses	31	10·06	32	9·69	31	9·65	94	9·80
Septic blister ..	3	6·00	3	6·00	5	5·40	11	5·73
Overall ..	106	9·42	110	9·50	104	9·19	320	

TABLE II.—*Overall Results for Patients not Receiving Preoperative Chemotherapy*

Post-operative Treatment Group					
No Chemotherapy		Oral Penicillin		Depot Penicillin	
No. of Patients	Average Healing-time (Days)	No. of Patients	Average Healing-time (Days)	No. of Patients	Average Healing-time (Days)
64	9·07	76	9·25	77	9·67

Patients who received no chemotherapy before operation were assessed separately (Table II). The overall average healing-time in the "depot" group was 0.4 and 0.6 day more than in the "oral" and "no chemotherapy" groups, respectively.

Chronic cases were placed on the same rota as acute cases and treated similarly; 13 (87%) were paronychia and 10 (66%) had received previous treatment by incision or penicillin or by both. The average healing-time was 12.3 days, although the average preoperative duration was 83.3 days, as Table III shows. Two (16.6%) gave cultures of *Staphylococcus aureus* sensitive to penicillin and erythromycin, 7 (58.3%) produced no growth, and 3 (25.1%) gave *Staph. aureus* resistant to penicillin but sensitive to erythromycin.

Bacteriological results are shown in Table IV. Of the 260 swabs taken from acute infections 220 (84.6%) produced growths of *Staph. aureus*, 37 (14.2%) gave no growth, 2 (0.8%) gave *Staph. albus*, and from 1 (0.4%) a strain of yeast was isolated. Of the cultures of *Staph. aureus* 183 (83%) were fully sensitive to penicillin, and 37 (17%) were penicillin-resistant. All were sensitive to erythromcyin.

Penicillin Blood Levels.—Of the 42 patients whose blood samples were examined 34 (81%) had bacteriostatic levels of penicillin. The specimens from 4 (9.5%) patients were contaminated or destroyed and 4 (9.5%) had no penicillin or very small amounts.

X-ray films revealed no bone infections.

TABLE III.—*Chronic Cases*

Type of Lesion	No.	Duration (Days)	Healing Time (Days)
Paronychia	13 (87%)	83·2 (average)	12·7 (average)
Onychia	1 (7%)	112	12
Subcutaneous abscess	1 (7%)	30	8
Overall ..	15	83·3	12·3

TABLE IV.—*Bacteriological Results*

	Staphylococcus aureus				Other Growth	No Growth	Total Cultures
	Penicillin-sensitive	Penicillin-resistant	Erythromycin-sensitive	Total			
Acute infections	183 (83%)	37 (17%)	220 (100%)	220	3	37	260
Chronic infection	2 (40%)	3 (60%)	5 (100%)	5	—	7	12

Complications.—Six patients had prolonged healing-times due to factors summarized in Table V—namely, inadequate surgery in three cases; a yeast infection, refusal to rest the part, and general uncleanliness in the others. Each had a deviation from the treatment method of its original category, perforce or through not attending, and therefore could not be legitimately included in one treatment group. However, an analysis including these cases, except No. 1, in their original categories showed no significant difference between the overall average healing-times of the different treatment groups.

An *allergic reaction* occurred in a patient who had a palmar abscess. While taking oral penicillin he developed a generalized irritative rash and swelling of the lips which was relieved by 50 mg. of diphenhydramine hydrochloride three times a day for a few days.

Occupation.—Table VI shows that more than half of the patients were unskilled workers, jute-workers, or housewives; groups which account for a high proportion of the population of Dundee. The remainder were distributed amongst engineering trades, miscellaneous skills, farm- and wood-workers, building and contracting trades, electricians,

TABLE V.—*Complications*

No.	Diagnosis	Healing Time (Days)	Details
1	Pulp abscess	189	Depot penicillin group. Yeast infection. Admitted for antibiotic and operative treatment. Large loss of pulp substance but good flexion finally
2	,, ,,	19	No chemotherapy group. Misdiagnosed and treated as septic blister. Given seclopen two days after operation. Discharged spontaneously
3	Palm ,,	30	No chemotherapy group. Misdiagnosed as septic blister. No extension seen at operation but further incision and seclopen given 5 days later
4	Paronychia	21	No chemotherapy group. Single incision inadequate. Double incision and removal of nail-base 10 days later
5	,,	45	No chemotherapy group. Robust farmer, declined to rest limb or attend for regular dressings. Repeatedly superinfected
6	,,	50	Depot penicillin group. Double incision and removal of nail-base adequate. Personal hygiene very poor

TABLE VI.—*Occupational Incidence*

Occupation	No.
Unskilled worker	73 (20·4%)
Jute-worker	73 (20·4%)
Housewife	55 (15·4%)
Housewife with other occupation	19 (5·3%)
Unemployed and school children	45 (12·6%)
Engineering trades	34 (9·5%)
Unclassified skills	29 (8·1%)
Farm-worker	12 (3·4%)
Wood-worker	11 (3·2%)
Building and contracting trades	3 (0·8%)
Electrician	3 (0·8%)
	357 (100%)

and schoolchildren. The low occurrence of electricians, 0.8%, is surprising in view of their frequent handling of small, sharp-pointed instruments and wire.

The preponderance of unskilled workers suggests that occupational interest and skill may be associated with personal attendance to cleanliness and well-being, whilst the hazards of the home or the housewives' degree of selflessness may be of a high degree.

Discussion

Penicillin assistance to localization in infections of the hand is generally accepted and has been supported by Gordon (1951) and Robins (1952). Post-operatively its value is not clear. Curr (1945) found the results of administering intramuscular penicillin to a few cases not encouraging;

Harrison *et al.* (1949), in a detailed study, concluded that systemic penicillin produced a significant reduction in the healing-time in pulp infections; Bolton *et al.* (1947) noted benefit in bony felons but not in simple pulp abscesses; Pilcher *et al.* (1948) questioned the best application of penicillin to infected hands, although acknowledging the antibiotic's general benefits; and a reduction in healing-time of acute paronychia, effected by intramuscular procaine penicillin and particularly by benethamine penicillin, has been shown by Williams *et al.* (1956). Bentley (1950) has advised post-operative penicillin for several days in infections of the hand. Bailey (1952) suggests intelligent selection of cases for chemotherapy rather than routine penicillin cover, and the use of the newer antibiotics if penicillin-resistant strains of *Staph. aureus* continue to increase. These conflicting opinions prompted the investigation.

Part of the solution to the epidemiological and surgical problems posed by the continued emergence of resistant staphylococci is suggested by the work of Clarke *et al.* (1952), who found that the greatest numbers of resistant staphylococci were in environments where most antibiotic treatment was given, and by the investigations of Blowers *et al.* (1955), which showed that where the routine administration of penicillin was stopped the proportion of resistant strains declined. These findings strengthen the belief that excessive use of penicillin is an important factor in reducing its value and that this may be restored by limiting administration to essential cases.

To deny a patient the possible benefits of penicillin demands sound proof of its dispensability. The reduction in the overall average healing-time of less than a quarter of a day in the "depot penicillin" group as compared with the "no chemotherapy" group, under the conditions of this investigation, does not justify the administration of penicillin post-operatively without a special reason.

The argument that the uncontrolled factor of preoperative chemotherapy in this series might selectively affect healing times is invalidated by the figures in Table II, which closely correspond to the overall figures (Table I) of the whole series, upon which a statistical analysis was carried out.

The distributions of the observed healing-times about the means are not symmetrical, and in order to justify the application of conventional tests of significance to the data the transformation factor $y=\sqrt{x+\frac{1}{2}}$ was applied, where x was the healing-time in days. This brought the distributions closer to normality without selectively affecting the variance. An analysis of variance on the transformed data for paronychia, onychia, pulp abscess, and other abscesses showed that the small differences in healing-time between the treatment groups could have arisen by chance on more than one occasion in 20 and thus did not achieve significance. However, the "depot penicillin" treatment effects for web abscess were significant at the 5% level, but there was no significant difference between the healing-time in the "no chemotherapy" and "oral penicillin" groups. The numbers in the dorsal (5), palmar abscess (2), and septic blister subgroups were too small for separate comparison.

TABLE VII.—*Results of Treatment of Web Abscess*

	No Chemotherapy	Oral Penicillin	Depot Penicillin
No. of cases ..	4	5	6
Average healing time (days) ..	11·5	12·2	7·3

Where $p<0.05$.

Table VII shows the results of the treatment of web abscess. The reduction of four days in the average healing-time of the "depot penicillin" group may be due to the laxity of the tissues in the web spaces, permitting ready access of a blood-borne antibiotic which an increase in tension, such as would occur around an abscess in a digit, might be sufficient to reduce. Even in these cases, however, the high blood levels obtained twice daily with seclopen seem to have been essential, and more cases are required to give confidence in the findings.

The success of surgery in chronic infections was striking. Although the average healing-time exceeded that of acute infections the results in this small series warrant further investigation into the timing of surgical intervention and the extent of drainage required, particularly in paronychia.

The six complicated cases clearly portray the consequences of misdiagnosis or mistimed surgery. In the most favourable circumstances Cases 2, 3, and 4 might have been saved one or two weeks of disability each. The presence of these three patients in the "no chemotherapy" group must be regarded as coincidental when the progress of the 106 others in this group is considered. The prolonged healing-time is readily explicable in each case by the factors outlined in Table IV. Lessons learned from these cases were usefully applied in the management of others, particularly at the stage of planning the incision.

Summary and Conclusions

A study of the post-operative care of 357 cases of sepsis of the hand is described. Three unselected treatment groups were obtained, receiving either no chemotherapy, oral penicillin, or intramuscular penicillin. The respective healing-times were 9.4, 9.5, and 9.2 days.

Careful clinical examination, accurate diagnosis, and precise surgery are of greater importance than routine chemotherapy. Indications for chemotherapy are suggested.

Some observations on infecting organisms, chronic lesions, and occupational incidence are made.

Routine post-operative penicillin does not hasten healing in septic lesions of the hand which require surgical treatment, provided that a careful technique is based upon anatomically accurate diagnosis.

Penicillin has been safely excluded from the post-operative environment of uncomplicated acute infections of the hand, and this may be a more fundamental counter to the emergence of resistant organisms than recourse to other antibiotics.

Possibly web abscess and threatened infection of the structures that move or support the hand are the only firm indications for chemotherapy, which will not act as a cover for misdiagnosis or inappropriate surgery.

I thank Mr. W. F. Walker for mentorial help at all stages of this work; Miss Rosemary J. Morton, of the Unit for Research on Climate and Working Efficiency, Oxford, for the statistical evaluations; and Dr. W. Shepherd, department of bacteriology, University of St. Andrews, for the bacteriological and blood investigations. The series was facilitated by the co-operation in organization and treatment methods of Sister Young and the nurses of the surgical out-patient department, Royal Infirmary, Dundee.

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CLINICAL TRIALS WITH BEPHENIUM HYDROXYNAPHTHOATE AGAINST HOOKWORM IN CEYLON

BY

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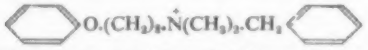
Copp, Standen, Scarnell, Rawes, and Burrows (1958) showed that members of a series of new quaternary ammonium compounds were active against a broad range of parasitic nematodes in laboratory and domestic animals. One of the most active compounds, bephenium embonate (benzyldimethyl-2-phenoxyethylammonium embonate), was shown by Rawes and Scarnell (1958) to be of value in the treatment of nematodiriasis in lambs.



The demonstration of high activity of bephenium salts against *Ancylostoma caninum* in dogs and cats (Copp *et al.*, 1958) led naturally to preliminary trials in London against hookworm infections in man. We are indebted to Professor A. W. Woodruff, of the Tropical Diseases Hospital, and Drs. D. H. Garrett and M. J. Andrewes, of the Dreadnought Hospital, for carrying out these trials. The results were encouraging and justified more extensive trials against heavier hookworm infections in Ceylon.

Tests in laboratory animals, including monkeys, showed that the toxicity of salts of bephenium was low. The less soluble salts, such as the 2-hydroxy-3-naphthoate and embonate, were poorly absorbed when given by mouth to human volunteers (Rogers, 1958).

Materials and Methods

Experiments with *A. caninum* in dogs and cats (Burrows, 1958), *Nippostrongylus muris* in rats, and *Nematospiroides dubius* in mice (Copp and Standen, 1958, in preparation) showed that bephenium halides, although more irritant, were appreciably more active against these organisms than were the less soluble hydroxynaphthoate and embonate. It was also found that equivalent anthelmintic activity was obtained when a proportion of the dose of halide was replaced by hydroxynaphthoate. On the basis of these observations, bephenium bromide, hydroxynaphthoate, and mixtures of these salts were selected for trial. The almost insoluble embonate was also tested.

Bephenium bromide and mixtures of bromide and hydroxynaphthoate were given as tablets, prepared so that they would disintegrate in the stomach within a few minutes of administration. The hydroxynaphthoate and embonate were given as tablets or as a sweetened and flavoured suspension in water. As a control group a proportion of the patients were treated with tetrachlorethylene. According to the general practice in Ceylon, it was administered together with a saline purge (Maplestone and Mukerji, 1939).

Faecal specimens were collected in ice-cream cartons. Patients whose stools contained hookworm ova on examination by direct smear were selected for treatment. Intercurrent infections with roundworm and whipworm, as seen by direct smear, were recorded. The number of hookworm eggs per millilitre of faeces was determined before treatment by the dilution-count technique as described by Stoll and Hausheer (1926). Four days after treatment a further specimen was collected and examined by direct smear. If positive for hookworm ova, a dilution count was made. If negative, the specimen was examined after concentration by the M.I.F.C. method (Sapero and Lawless, 1953; Blagg, Schloegel, Mansour, and Khalaf, 1955). All counts were made in duplicate.

The effect of treatment was assessed by calculation of the percentage reduction in egg count. An arbitrary figure of 200 eggs/ml. was awarded to those specimens which were negative on direct smear but positive on concentration.

In some instances the stools passed after treatment were washed through a No. 60 sieve and the hookworms recovered for identification of species.

Patients were treated at the General Hospital and Lady Ridgeway Children's Hospital in Colombo, and at the General Hospital in Negombo. A group of Tamil labourers and their children were treated under field conditions at the Sapumalkande rubber estate, Dehiowita. Patients were selected for treatment with the different preparations of bephenium by a random method. A special group of children with infections which had proved resistant to successive treatments with tetrachlorethylene were given multiple doses of bephenium hydroxynaphthoate ("alcopar") at Ragama Convalescent Home.

Bephenium salts were given early in the morning on an empty stomach, and no food was allowed until at least two hours after the dose. No purge was given after the dose. One group of patients were given three doses on one day; the second and third doses were spaced between meals. Patients in hospital were treated with piperazine citrate syrup ("antepar") on the day before administration of a bephenium salt. Estate labourers were given no pre-treatment with piperazine. Throughout this report all doses of bephenium salts are expressed in terms of base: 1 g. of bephenium base is contained in 1.31 g. of bephenium bromide, 1.73 g. of bephenium hydroxynaphthoate, and 1.75 g. of bephenium embonate.

The weight of infection with hookworm before treatment varied greatly among the 284 patients treated. An analysis of the distribution of egg counts (Fig. 1) shows that patients admitted to hospital had a significantly higher mean rate of infection than the labourers at the rubber estate. The random selection of patients for the separate treatment groups resulted in fairly evenly distributed proportions of heavy, moderate, and light infections.

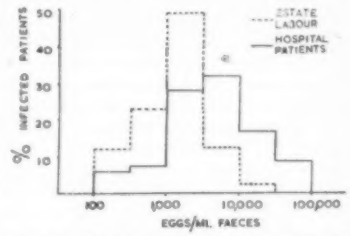


FIG. 1.—Distribution of the number of hookworm eggs/ml. of faeces from 132 estate labourers and 109 hospital patients in Ceylon.

Effect of Bephenium Salts in Treatment of Hookworm Infection

Bephenium Hydroxynaphthoate

The first few patients were treated with small doses of bephenium, the size of the dose being adjusted in accordance with body weight. It soon became apparent that the less soluble salts had no toxic side-effects even when given in doses as large as 200 mg./kg. It was also clear that the small doses administered to children on the mg./kg. basis had no appreciable effect on the egg count. As a result of these preliminary tests it was concluded that a single dose of less than 2 g. in the child and in the adult was insufficient, and subsequently a standard dose of 2 to 3 g. of bephenium

base was administered to all patients irrespective of weight and age. The drug has a bitter taste, but was accepted by both adults and children. Table I shows the results obtained with patients in hospital who were given single doses of bephenium hydroxynaphthoate. Hookworms were recovered from the stools of patients given as little as 1 g.

TABLE I.—*Effect of Single Doses of Bephenium Hydroxynaphthoate or Tetrachlorethylene against Hookworm (Necator americanus)*

	Bephenium Hydroxynaphthoate*			Tetrachlorethylene	
	0·5–1·5 g.	2 g.	2·5–3 g.	5 m. (0·3 ml.) Children	30–40 m. (1·8–2·4 ml.) Adults
No. of patients treated	6	16	29	5	11
,, in whom degree of infection was reduced	3	14 (88%)	27 (93%)	2	9 (82%)
,, in whom infection was reduced by 100–75%	1	11 (69%)	13 (45%)	0	8 (73%)
,, in whom infection was reduced by 74–25%	2	3 (19%)	11 (38%)	1	0
,, in whom infection was reduced by 24–0%	3	2 (12%)	5 (17%)	4	3 (27%)
Initial weight of infection (eggs/ml.)	37,000–1,200	44,000–200	44,400–200	6,400–400	31,700–100
Mean reduction in count	28%	78%	64%	12%	70%

* Dose in terms of base.

given daily for four successive days; those who still retained some degree of infection and were still in hospital were given a further seven-day course of treatment. The results are given in full in Table III.

The effect of four 2-g. doses on the faecal egg count of one 6-year-old child is shown in Fig. 2. This child had advanced cirrhosis of the liver (confirmed by biopsy) and gross ascites. He was considered by the physician to be unsuited for treatment with tetrachlorethylene. Bephenium greatly reduced the egg count, and no toxic side-effects of any kind were observed. After treatment, hookworms were recovered from the stools. Examination of this child 10 weeks after treatment showed that the stools were free from hookworm ova.

In order to study the effectiveness of bephenium hydroxynaphthoate under field conditions, trials were carried out in a group of 132 Tamil labourers and their

of bephenium even if the subsequent egg count showed no significant reduction. All hookworms isolated from the stools were identified as *Necator americanus*.

Twenty-seven patients were given 2 g. of hydroxynaphthoate three times on one day. The results are shown in Table II.

A group of children aged from 4 to 10 years were treated with multiple doses of bephenium hydroxynaphthoate. All had been admitted to hospital in a critical condition, suffering from malnutrition, anaemia, severe gastro-enteritis, and hookworm infection. Before treatment with bephenium their general condition had been improved by intravenous fluids, iron, and vitamins, but they were still passing several fluid stools each day. Some of the children had already received one or more treatments with tetrachlorethylene, but their stools still contained hookworm ova. Because of their precarious fluid balance, others were regarded by the physician as being too ill to be given tetrachlorethylene and subsequent purgation. In view of the persistent intestinal hurry, it was considered rational to administer more than one dose of bephenium. Doses of 2 g. were

TABLE II.—*Effect of Multiple Doses of Bephenium Hydroxynaphthoate against Hookworm. Three Doses Each of 2 g. (Base) were Given on One Day*

Sex	Age	Hookworm Eggs/m.l. Faeces		
		Initial	Final	Reduction (%)
M	Adult	27,000	14,400	48
M	,,	24,300	1,900	92
M	,,	22,800	1,700	93
F	5	15,700	200	99
M	Adult	15,200	2,800	82
M	,,	15,100	1,300	91
M	,,	15,100	800	95
M	,,	8,000	1,800	80
F	6	7,600	0	100
F	5	6,700	200	97
M	Adult	5,000	0	100
M	,,	3,700	0	100
M	,,	2,000	500	75
M	,,	1,700	0	100
M	,,	1,600	300	82
M	,,	1,300	0	100
M	,,	1,200	400	67
M	,,	1,000	2,500	Failure
M	,,	800	200	75
M	,,	700	200	72
M	,,	600	0	100
F	6	400	0	100
M	Adult	300	0	100
M	,,	200	300	Failure
M	,,	200	200	,,
M	,,	100	0	100
M	,,	100	0	100
No. of patients treated				27
,, in whom degree of infection was reduced				24 (89%)
No. in whom infection was reduced by 100–75%				21 (78%)
No. in whom infection was reduced by 74–25%				3 (11%)
No. in whom infection was reduced by 24–0%				3 (11%)
Initial weight of infection (eggs/g. faeces)				27,000–100
Mean % reduction in count				79

TABLE III—*Effect of Multiple Doses of Bephenium Hydroxynaphthoate against Hookworm in Children. Doses of 2 g. (Base) were Given Daily for Four Days; Some Patients Received an Additional Course of Treatment for Seven Days*

Sex	Age Years	Hookworm Eggs/ml. Faeces				
		Initial	After 4 Doses		After a Further 7 Doses	
			Final	Reduction (%)	Count	Total Reduction (%)
M	6	62,800	6,900	89		
F	10	50,000	800	98		
M	4½	14,800	0 conc.	100		
M	7	11,800	1,000	92		
M	6	9,000	+ direct (no count)		0 conc.	100
F	7	8,400	200	98		
M	5	7,700	400	95		
F	7	6,400	900	86	0 conc.	100
M	7	5,000	900	82	300	94
F	6	4,700	2,800	40		
M	4	3,200	400	87	900	72
M	4	3,000	300	90		
M	6	2,800	1,900	32	900	68
F	4	2,400	0 conc.	100		
M	10	2,400	0 ,,	100		
M	8	1,600	400	75	300	82
F	4	1,200	200	83		
F	8	1,200	3,300	0		
M	8	700	900	0	600	14
No. of cases			18		7	
No. in which infection was reduced			16 (89%)		7	
No. reduced by 100–75%			14 (78%)		4	
No. reduced by 74–25%			2 (11%)		1	
No. reduced by 24–0%			2 (11%)		1	
Mean reduction in count			75%		76%	

" 0 conc." indicates negative on concentration.

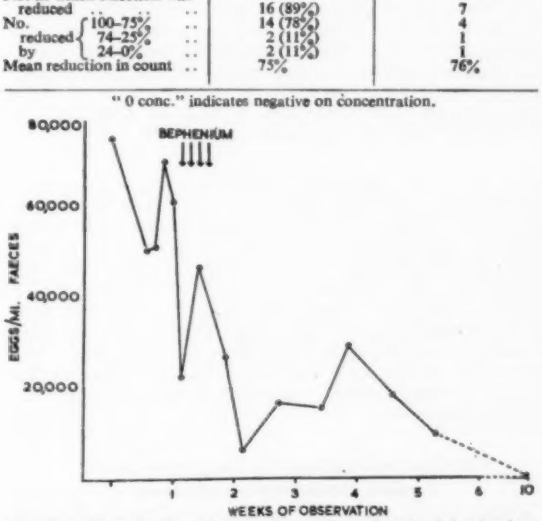


FIG. 2.—Effect of four doses each of 2 g. (base) of bephenium as hydroxynaphthoate on the faecal egg count. The drug was given to a child with heavy hookworm infection, advanced cirrhosis of the liver, and ascites.

families employed at the Sapumalkande rubber and tea estate near Dehiowita. The patients were divided into six treatment groups, which were given: (1) 3 g. of bephenium alone, as a suspension in water; (2) 3 g. of bephenium, as suspension, one hour after a dose of 1 oz. (30 g.) of magnesium sulphate in water; (3) 3 g. of bephenium, as suspension, together with the saline purge; (4) 3 g. of bephenium together with 1 fl. oz. (28 ml.) of piperazine citrate syrup; (5) 1 g. of bephenium, as suspension, daily for four or five days; (6) 30 minims (1.8 ml.) of tetrachlorethylene together with the saline purge. The results are shown in Table IV.

TABLE IV.—*Effect of Bephenium Hydroxynaphthoate or Tetrachlorethylene against a Series of* 132 *Hookworm Infections in the Field*

	Bephenium Hydroxynaphthoate*					T.C.E.
	3 g.	3 g. Preceded by Purge	3 g. with Purge	3 g. with Piperazine 1 fl. oz. (28 ml.)	1 g. Daily for 4–5 Days	30 m. (1·8 ml.) with Purge
No. of patients treated	28	20	19	32	15	18
,, in whom degree of infection was reduced	24 (86%)	17 (85%)	15 (79%)	27 (84%)	14 (93%)	14 (78%)
No. in whom infection was reduced by 100–75%	16 (57%)	10 (50%)	5 (26%)	20 (62%)	11 (74%)	10 (55%)
No. in whom infection was reduced by 74–25%	7 (25%)	5 (25%)	6 (32%)	8 (25%)	2 (13%)	3 (17%)
No. in whom infection was reduced by 24–0%	5 (18%)	5 (25%)	8 (42%)	4 (13%)	2 (13%)	5 (28%)
Initial weight of infection (eggs/ml.)	6,600–100	22,300–200	14,500–200	11,500–100	7,200–400	11,900–200
Mean reduction in count	66%	67%	41%	74%	72%	61%

* Dose in terms of base.

Bephenium Bromide

This salt has an extremely bitter taste, and was administered with difficulty because of its nauseating properties. Of the seven patients who were given 1.25 g. to 2.5 g. of the drug as tablets, two vomited almost immediately. Reduction of egg count in the stools was observed in only three of the patients, and the mean reduction for the series was 25%. The use of this salt was discontinued.

Mixtures of Bephenium Bromide and Hydroxynaphthoate

Small groups of patients were treated with doses of 2 to 2.5 g. of mixtures of bephenium bromide and hydroxynaphthoate in the proportions of 2:1, 1:1, and 1:2 respectively. The effectiveness of the dose was directly proportional to the amount of hydroxynaphthoate in the mixture. With a mixture containing 2 parts of bromide to 1 part of hydroxynaphthoate the mean reduction in egg count was 55% (4 cases); with equal proportions of salts this figure was 64% (5 cases); with a mixture of 1 part of bromide to 2 parts of hydroxynaphthoate the reduction was 70% (5 cases), a figure which is similar to that given by the hydroxynaphthoate alone. Mixtures containing the bromide caused nausea, and since they offered no advantage in effectiveness their use was discontinued.

Bephenium Embonate

Bephenium embonate was the least soluble of the compounds investigated. It was tested at doses of 0.75 to 5 g. in a series of 18 patients whose egg counts ranged from 83,800 to 200 eggs/ml. There was no correlation between anthelmintic effect and dose. Twelve of the patients (67%) showed a reduction of egg count, and the mean reduction for the series was 55%. The proportions of patients with reductions in egg counts of 100–75%, 74–25%, and 24–0% were 50%, 17%, and 33% respectively. These results compared unfavourably with those obtained with the hydroxynaphthoate.

Effect of Bephenium Hydroxynaphthoate Against Roundworm Infections

A high proportion of the persons at the Sapumalkande estate selected for treatment with bephenium for hookworm were intercurrently infected with roundworm and whipworm. Most of the roundworm infections were very heavy; the majority of stools examined by direct smear were seen to contain numerous ova. No attempt was made to evaluate the number of roundworm ova per millilitre of faeces, and the effect of the drug was assessed by the presence or absence of eggs in direct smears at follow-up examinations.

Table V shows the results obtained against the intercurrent *Ascaris* infections in the patients treated for hookworm with bephenium. Whilst a marked effect was seen against roundworm, there was no significant action against whipworm following a single 3-g. dose of bephenium.

TABLE V.—*Effect of Bephenium Hydroxynaphthoate or Tetrachlorethylene against a Series of* 101 *Cases of Ascariasis in the Field*

Treatment (Dose in Terms of Base)	No. of Patients Positive on Direct Smear		
	Before Treatment	After Treatment	% Cleared
3 g. bephenium alone	22	5	77
3 ,, ,, preceded by saline purge	16	7	56
3 ,, ,, together with saline purge	13	6	54
3 ,, ,, ,, 1 fl. oz. (28 ml.) piperazine citrate syrup	24	11	54
1 g. bephenium daily for 4 or 5 days	10	1	90
30 m. (1·8 ml.) tetrachlorethylene together with saline purge	16	12	25

Discussion

Tetrachlorethylene has been used for many years in the treatment of hookworm infection. It is cheap and effective and the toxicity is low. It is best administered in the morning, following a saline purge the night before. Two hours after the dose, a second purge is given to remove the tetrachlorethylene and thereby avoid absorption. This procedure rarely fails to remove most of the hookworms. For mass treatment in the field, in out-patient departments, and in crowded hospitals in the tropics with limited nursing staff, these optimal conditions for treatment are often impracticable. Maplestone and Mukerji (1939) introduced a method in which the tetrachlorethylene is given together with the saline purge in a single dose; this is the method most widely used at present in Ceylon. Mass treatment for many years by this practical method has led to a considerable decrease in weight of infection in estate labour.

Tetrachlorethylene is unpleasant to take and often produces dizziness and nausea. These side-effects and the necessity for abstinence from food until the purge has taken effect usually involve absence from work on the day of treatment. In addition, roundworm infection is often found in association with hookworm. Tetrachlorethylene has little anthelmintic value against roundworms, although it stimulates them and may constitute a danger when massive infections are present.

In patients suffering from heavy hookworm infection with severe anaemia, malnutrition, and diarrhoea the condition of the circulation is sometimes such that it is inadvisable to endanger the precarious fluid balance by giving a saline purge. Treatment with tetrachlorethylene must be withheld until the condition of the patient can be improved. This is an important consideration in the treatment of children, and the small dose of tetrachlorethylene which can be given safely is often valueless for the expulsion of the hookworms (Table I). These characteristics of tetrachlorethylene have stimulated the search for new remedies. The results obtained in the present clinical trial with bephenium hydroxynaphthoate show that this drug overcomes many of the disadvantages associated with the use of tetrachlorethylene. However, in view of the bitter flavour of bephenium it is desirable to withhold treatment from patients with severe vomiting and dehydration until the fluid balance has been restored by intravenous infusion.

Table I shows that a single dose of 2 to 3 g. of bephenium hydroxynaphthoate was at least as effective as 30 to 40 min. (1.8 to 2.4 ml.) of tetrachlorethylene, the dose used for treatment in Ceylon hospitals. Adult male patients weighed about 100 lb. (45.4 kg.) and were given 40 min. (2.4 ml.); adult females weighed about 80 lb. (36.3 kg.) and were given 30 min. (1.8 ml.). The larger dose of 60 min. (3.6 ml.) recommended by Maplestone and Mukerji (1939) was not used because previous experience in Ceylon had shown that it often caused dizziness and other unpleasant side-effects. The children recorded in Table I were 5 to 6 years old and weighed between 17½ and 26 lb. (7.9 and 11.8 kg.). They were given 5 min. (0.3 ml.) of tetrachlorethylene, which was ineffective.

When three doses of bephenium hydroxynaphthoate, each containing 2 g. of base, were given on the same day to a group of 27 patients, the effect was similar to that produced by the single dose containing 2 to 3 g. when assessed by the mean percentage reduction in egg count. Some of the patients were children who were passing several fluid stools a day, and the three-dose treatment had a greater effect upon their hookworm infection and general condition than would have been expected from a single dose.

The results in Table III were obtained with 18 children who were also suffering from chronic diarrhoea. Most of the children had been given treatment with ineffective doses of tetrachlorethylene on several occasions. After four successive daily doses of 2 g. of bephenium hydroxynaphthoate, 16 (89%) showed considerable reduction in egg count. All the children were passing formed stools, and their general condition had much improved. Five of the seven children who remained in hospital showed a further reduction in egg count after an additional course of seven doses of 2 g. One child, who was still passing hookworm ova in his stools, subsequently had a recurrence of diarrhoea. This was controlled by a further course of treatment of three doses of 2 g. in one day, which reduced the egg count to insignificant proportions.

It is doubtful if the result in this group of children could have been achieved with any treatment other than bephenium. Multiple-dose treatment with bephenium would appear to be particularly advantageous in hookworm infection associated with intestinal hurry; it is reasonable to suppose that greater opportunity for contact of the drug with the worms is provided by a succession of doses. The effect of bephenium in controlling the diarrhoea of patients infected with hookworms is of special interest because the drug sometimes caused looseness of the bowel when given in equivalent doses to normal volunteers in England (Rogers, 1958).

Table IV shows that when a saline purge was given one hour before a dose of 3 g. of bephenium as hydroxynaphthoate the results obtained were the same as those after the drug was given alone. On the other hand, when the purge was given together with the bephenium the results were much less satisfactory. It is likely that the drug was removed from its site of action before it had exerted its full effect. It is possible that the purge induced conditions similar to those in children with diarrhoea (Table III) and reduced the opportunity for contact of the drug with the worms.

The results obtained when a dose of 1 g. of bephenium was given daily for four to five days were similar to those recorded for a single dose of 3 g.

In earlier experiments with *N. muris* in rats it was observed that piperazine exerted an effect antagonistic to the anthelmintic action of bephenium halides. It was not known whether this antagonism would occur in hookworm infections in man. In the group of patients treated with bephenium hydroxynaphthoate and piperazine (Table IV) it was clear that the activity of bephenium was unimpaired.

It has been shown (Table V) that bephenium hydroxynaphthoate has a marked effect against roundworms. No additive effect was observed when it was given together with piperazine.

For assessment of results in these trials one duplicate egg count was made before and after treatment. It was appreciated that daily egg counts in any individual would show a marked variation, and that comparison of counts at two points several days apart might be suspect. In trials of drugs of doubtful efficacy against hookworm the arbitrary selection of two points in the daily variation sequence may lead to erroneous conclusions (Goodwin and Standen, 1958). This would be true if results of treatment related to single or small numbers of cases, but where overall reduction can be achieved in a series of reasonable length the anthelmintic effect becomes apparent.

Our results show quite clearly that bephenium hydroxynaphthoate is highly effective in the treatment of hookworm infections. This is most apparent in those cases where very heavy infections were cured, or the egg count was reduced to insignificant proportions. However, the effect of drug treatment is not shown so satisfactorily in cases where the infection is light and where only partial reduction in egg count has been obtained. Daily variation apart, this is largely due to the fact that any dilution egg-count technique is insufficiently sensitive to provide accurate information where the number of eggs in the faecal suspension is small. It has been shown by Beaver (1955) that 200–500 ova per ml. of faeces may be produced by not more than two female *N. americanus*. When such small numbers of worms are present the opportunity for variation in daily egg count is much increased. In these instances the application of a multiplication factor of 100 or 200 to the number of eggs seen in a small measured volume affords too wide a margin of error for accurate conclusions to be drawn.

Summary

Bephenium, a new anthelmintic, was compared with tetrachlorethylene in the treatment of 284 cases of hookworm infection in Ceylon.

Bephenium hydroxynaphthoate was selected as the most suitable salt. A single dose of 2 or 3 g. of base, or multiple doses given on successive days or three times on the same day, compared favourably in effectiveness with tetrachlorethylene.

No toxic side-effects were observed when large doses of bephenium were given.

Bephenium hydroxynaphthoate was particularly suitable for the treatment of patients with advanced anaemia, diarrhoea, and heavy hookworm infections because of its low toxicity and because no purge was necessary.

Bephenium hydroxynaphthoate was also effective against roundworm, which was present as a concurrent infection in 85 of the patients treated with this drug. Tetrachlorethylene was ineffective against roundworm in 16 patients treated.

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EXCRETION OF BEPHENIUM SALTS IN URINE OF HUMAN VOLUNTEERS

BY

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Goodwin, Jayewardene, and Standen (1958) have shown that bephenium salts were effective for the treatment of hookworm in man. Of the various compounds used for clinical trials in Ceylon, bephenium hydroxynaphthoate ("alcopar") was the most active, the embonate and bromide being considered unsatisfactory for clinical use. No toxic side-effects were observed when large doses of the hydroxynaphthoate were given. The present paper describes the urinary excretion rates of bephenium salts in volunteers in Britain.

Determination of Bephenium in Urine

The concentration of bephenium in urine was measured by means of a modification of the methyl orange dye–lake procedure. This method was supplied by Dr. S. R. M. Bushby, of the Wellcome Research Laboratories, Beckenham.

Reagents.—Ethylene dichloride:—the solvent was shaken with activated carbon, filtered, washed with 1/5 of its volume of N/1 NaOH and then washed twice with an equal volume of distilled water; it was then filtered to remove residual water. *Methyl orange solution:*—a saturated solution of methyl orange was prepared in 0.5 M boric acid, and washed with an equal volume of ethylene dichloride. *Acid alcohol:*—2 ml. of concentrated HCl was added to 100 ml. of absolute ethanol. *Solid sodium chloride. 40% w/v Sodium hydroxide solution.* Glassware was washed in very dilute detergent, well rinsed, washed in dilute HCl, and then in distilled water. Acetone was not used for drying glassware. Failure to observe these precautions resulted in high "blank" values.

Procedure.—1 ml. of urine was pipetted into a tube and 300 mg. of solid sodium chloride was added. The tube was shaken to saturate the solution and 8 ml. of ethylene dichloride was added. The tube was stoppered, the contents were shaken for 10 minutes and then centrifuged; 6 ml. of the lower (solvent) layer was removed into a clean tube. 0.4 ml. of the methyl orange reagent was added and the tube shaken thoroughly. The excess of methyl orange solution was removed with a Pasteur pipette after centrifuging; 5 ml. of 40% sodium hydroxide was added and mixed by a brief shaking. The tube was centrifuged and 4 ml. of the upper (solvent) layer was removed into a clean tube. 0.4 ml. acid alcohol was added and the absorption was measured in an absorptiometer at 540 mμ. "Blanks" were prepared, using water instead of urine, and treated in the same way. A standard curve was prepared with solutions of bephenium hydroxynaphthoate of known strength, and the basic substances excreted in the urine were expressed as bephenium.

Excretion of Bephenium after Oral Administration in Man

The preparations used were: bephenium bromide as compressed tablets each containing 500 mg. of base, and bephenium embonate and hydroxynaphthoate in the form of sweetened and flavoured emulsions containing 500 mg. of base per fl. dr. (140 mg. per ml.).

The volunteers were healthy normal adults. For each excretion study the subject was given the dose orally, followed by 100 ml. of diluted orange squash. Urine was collected at each emptying of the bladder, and the volume and time were noted. The urines were refrigerated until used for analysis; no preservatives were added. The Table shows the percentage of the dose recovered.

Figs. 1 and 2 show the cumulative excretion rates of the drug and its metabolites after doses of bephenium bromide, embonate, and hydroxynaphthoate. Fig. 3 shows the excretion rates of bephenium hydroxynaphthoate after the administration of 2.5 g. base daily on successive days. It will be seen that the excretion of bephenium and its

Dosage and Percentage Excretion of Bephenium in Human Volunteers

Sex	Age	Compound	Dose in g. Base	% of Dose Recovered in 24 Hours
M	29	Bromide	1	0·79
M	25	,,	1	0·72
M	31	,,	1	0·59
F	19	Embonate	1	0·04
M	19	,,	1	0·06
M	26	,,	3	0·05
M	27	,,	3	0·06
M	40	,,	3	0·06
M	32	Hydroxynaphthoate	1	0·52
F	25	,,	1	0·25
M	43	,,	3	0·18
M	38	,,	3	0·22
M	39	,,	3 doses of 2 g. in one day	0·44
M	36	,,	,, ,,	0·21
M	28	,,	,, ,,	0·23
M	32	,,	2·5 g. daily for 4 successive days	1st day 0·05 2nd ,, 0·12 3rd ,, 0·10 4th ,, 0·26
M	46	,,	,, ,,	1st ,, 0·14 2nd ,, 0·27 3rd ,, 0·19 4th ,, 0·23
M	44	,,	2·5 g. daily for 3 successive days	1st ,, 0·05 2nd ,, 0·14 3rd ,, 0·06

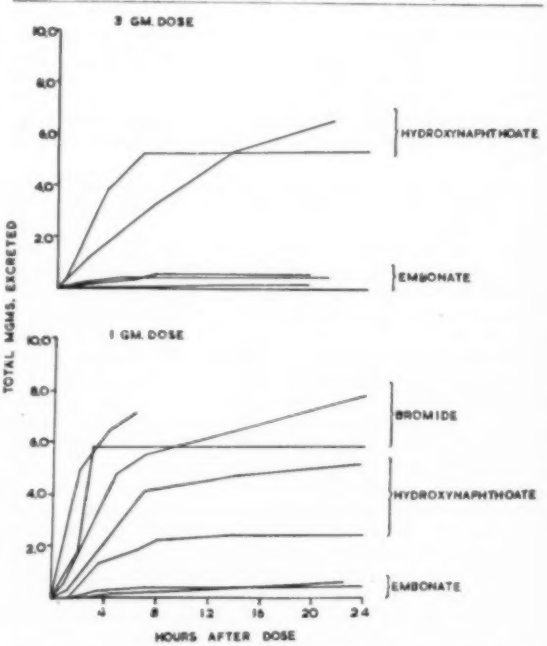

FIG. 1.—Cumulative excretion rates of bephenium bromide, embonate, and hydroxynaphthoate in human volunteers after a single dose.

metabolites in man is low. The bromide, which is soluble to the extent of 30% in water, was excreted in larger amounts than the less soluble hydroxynaphthoate. The almost insoluble embonate was excreted in still smaller amounts.

As found by Goodwin *et al.* (1958) in Ceylon, the bromide gave rise to nausea and vomiting. Side-effects from the hydroxynaphthoate and embonate were slight; mild diarrhoea sometimes occurred after a single dose, and some volunteers complained of borborygmi. The same effects occurred daily after repeated doses of hydroxynaphthoate. Some subjects did not complain at all, and the intensity of side-effects was not correlated with the amount of drug excreted in the urine. Side-effects ceased completely 24 hours after the dose. It is interesting to note that no side-effects were observed after treatment with embonate or hydroxynaphthoate in Ceylon, where many of the subjects were already suffering from gastro-enteritis. This might perhaps be explained by dietary differences; the digestive tracts of those accustomed to hot curries may well be less sensitive than those of subjects who partake of less-stimulating foods. It is also of interest that no such side-effects were encountered among mentally defective children in an institution in Britain where the drug was tested for its action on whipworm infection.

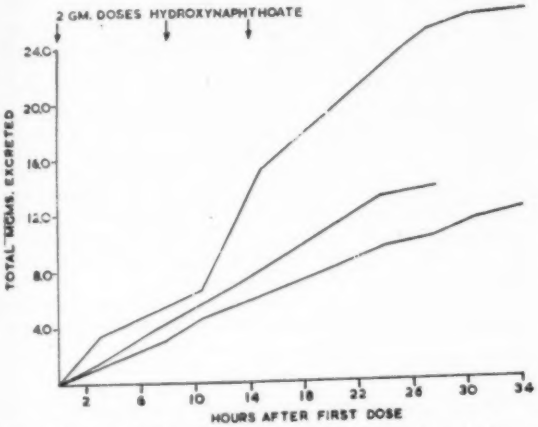

FIG. 2.—Cumulative excretion rates of bephenium hydroxynaphthoate in human volunteers after three single doses in one day.

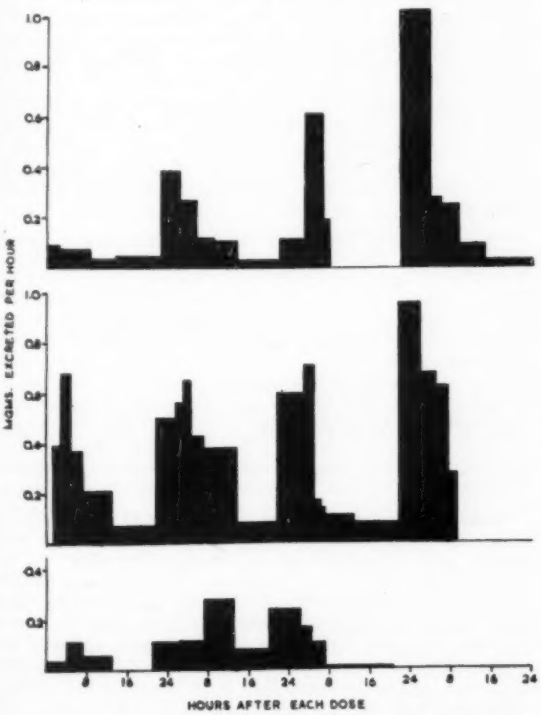

FIG. 3.—Hourly excretion rates of bephenium hydroxynaphthoate in human volunteers after successive daily doses.

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Medical Memoranda

Thrombocytopenic Purpura Apparently Due to Tablets Containing Salicylamide and Mephenesin ("Arthripax")

A woman aged 64 was seen by me on October 16, 1958, suffering from widespread purpura with subcutaneous ecchymoses and haemorrhages into the tongue. The rash had begun to appear ten days before and had gradually increased in severity. On inquiry it was found that she had been taking two tablets of arthripax three times daily for about three weeks on account of a painful arthritis of the left knee.

Apart from the haemorrhages physical examination was negative, and there was no previous history of important illness. The blood count was as follows: total red cells 2,977,000 per c.mm.; haemoglobin, 56% (8.3 g./100 ml.); colour index, 0.94; total white cells per c.mm., 6,900. Differential count: polymorphonuclears, 63.5%; lymphocytes, 30.0%; large mononuclears, 6.5%; eosinophils, nil; basophils, nil; aniso- and poikilocytosis, slight; nucleated red cells, nil; platelets, less than 10,000 per c.mm.

The patient, who was ambulant, was told to stop taking the tablets and sent home to rest. When the result of the blood count was received a few hours later her doctor was warned by telephone to report at once if her condition deteriorated, so that she could be admitted immediately. In fact the patient made an uninterrupted recovery; no new haemorrhages appeared and the existing ones gradually resolved.

On October 30 she was well except for some breathlessness on exertion. The blood count then was: total red cells, 2,730,000 per c.mm.; haemoglobin, 58% (8.6 g./100 ml.); colour index, 1.04; total white cells, 6,300 per c.mm. Differential count: polymorphonuclears, 61%; lymphocytes, 29%; large mononuclears, 10%; eosinophils, nil; basophils, nil; aniso- and poikilocytosis, fairly marked; nucleated red cells, nil; platelets, 173,000 per c.mm.

On November 28 the blood count was as follows: total red cells 3,740,000 per c.mm.; haemoglobin 70% (10.4 g./100 ml.); colour index, 0.94; total white cells 5,900 per c.mm. Differential count: polymorphonuclears, 70.0%; lymphocytes, 23.5%; large mononuclears, 5.0%; eosinophils, 1.5%; basophils, nil; aniso- and poikilocytosis, nil; nucleated red cells, nil; platelets, 179,000 per c.mm.

Arthripax tablets contain salicylamide 5 gr. (0.32 g.), mephenesin 1 gr. (65 mg.), aluminium glycinate 1½ gr. (0.1 g.). The dose of both drugs is well within that which is considered to be safe, and the makers tell me that they have not heard of similar cases.

The question arises whether mephenesin or salicylamide was responsible, it being assumed that the patient had some idiosyncrasy. Both drugs contain a benzene ring. An orthopaedic colleague has told me of a case of purpura following mephenesin administration some years ago, but

was unable to give details. Salicylates are known very rarely to cause thrombocytopenic purpura. It is assumed that in this case a mild inhibition of red-cell production also occurred and accounted for the anaemia. Although no studies of haemolysis or liver function were made, the case seems worthy of a brief report so that prompt action may be taken in similar cases before platelet counts are reduced to such dangerous levels.

ROBERT PLATT, P.R.C.P.,
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Traumatic Fore-quarter Avulsion

Avulsion of the entire fore-quarter with survival is uncommon enough to justify the record of the following case.

CASE REPORT

At 3.30 a.m. on February 21, 1951, the sleeve of a Polish mine-worker aged 43 was caught in the conveyer belt and the left arm torn off. He was brought to hospital at about 5.30 a.m. in a pulseless condition due to shock. He was bleeding a little, but did not appear to have lost nearly as much blood as might have been expected. He was admitted to the wards, and after resuscitation at 6.30 a.m. the blood pressure was found to be 110/70 mm. Hg. At 9.30 a.m. he was given an anaesthetic and taken to the operating theatre.

On removal of his clothing the left upper limb was found to be missing from a large skin envelope. The wound, which extended from the middle line of the back from the level of the sixth cervical spine obliquely downwards to the outer side of the left nipple and for an inch or so below, was explored, and it was found that the clavicle had been fractured about its centre and the outer half of the clavicle, the entire scapula, and the left arm had been avulsed. All the muscles had retracted and the bony thorax was bare. The brachial plexus was not seen, but the subclavian vessels were sought for and ligated. The subclavian artery had been torn at about the spot where it becomes the axillary artery, and bleeding had been arrested by clotting and retraction of the vessel. The rough end of the fractured clavicle was trimmed and the wound closed with a continuous stitch after providing for drainage. There was some doubt about the viability of the skin, and as much as possible was retained in case of sloughing. From the time of admission until 6.15 p.m. 3 pints (1.7 litres) of blood were administered. At that time there was only minimal oozing and the blood pressure was 134/80, and the pulse rate 100. Apart from a little sloughing of the skin, which required trimming on March 12, the patient's progress from this time was uninterrupted. On the day following the accident it was noticed that he had a Horner's syndrome. On March 29 the wound had healed and he was discharged.

D. S. PRACY, F.R.C.S.Ed.

Unusual Length of a Plasmodium ovale Infection

Relapses of *Plasmodium ovale* infection are known to occur up to two years. A case has been reported by Jeffery *et al.* (1954) in which relapses with the Donaldson strain of this malarial parasite continued up to three and a half years. In the following case a relapse due to *P. ovale* occurred 52 months after possible exposure.

CASE REPORT

The patient, an Englishman aged 31, was admitted to hospital on June 24, 1957, with a history of severe throbbing occipital headache, vomiting, rigor, and fever the previous day. He had been getting attacks of headaches periodically every fortnight or so during the previous four years. He served in the British Forces at Kaduna, Nigeria, from July, 1951, to February, 1953. In September, 1952, he suffered from an attack of malaria and was treated in the Military Hospital at Kaduna. He took prophylactic proguanil every day until he arrived home in February, 1953.

On physical examination he looked ill but his temperature was normal. Systematic examination did not reveal any abnormality. A day after admission his temperature rose to 104° F. (40° C.), initiated by rigor. A blood film showed a heavy infection with *P. ovale*. Some of the red cells contained two or three ring forms. With prolonged staining Schüffner's dots were seen. The schizonts contained 8 to 10 merozoites arranged irregularly. (Diagnosis was confirmed by Professor P. C. C. Garnham.)

After a full course of chloroquine phosphate the patient has become symptomless, except for migraine.

COMMENT

This patient's history excludes any possibility of reinfection with malaria during the 52 months he lived in the British Isles. There seem to be no clinical grounds for regarding the headaches which occurred at fortnightly intervals as other than simple migraine. The headaches which necessitated his admission to hospital were accompanied by rigor and fever, and appeared clinically to be the first attack of malaria since September, 1952. A relapse of *P. ovale* infection has been shown to be accompanied by 18 to 20 merozoites (Garnham *et al.*); in this patient they numbered 8 to 10. This fact, combined with the clinical evidence, seems to indicate a primary infection after a prolonged interval rather than a simple relapse. Whichever interpretation is accepted, 52 months is the longest period recorded.

I am indebted to Professor P. C. C. Garnham and Dr. E. C. Hutchinson for their advice and help.

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Medical Registrar,
City General Hospital, Newcastle (Staffs).

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The home population of England and Wales as at June 30, 1958, was 45,109,000, of whom 21,744,000 were males and 23,365,000 were females, according to the Registrar-General's latest estimates. The total is 202,000 more than in mid-1957. Within the conurbations there has been a continuation of the movement from the centre to more open residential areas outside. Thus the Administrative County of London lost 29,000 between 1957 and 1958, and other losses were in Birmingham C.B. (8,000), Liverpool C.B. (6,300), Manchester C.B. (5,100), Newcastle upon Tyne C.B. (2,700), Wolverhampton C.B. (2,100), East Ham C.B. (1,800), and Salford C.B. (1,700).

Reviews

THE REDISCOVERY OF NEOMYCIN

Neomycin: Its Nature and Practical Application. Edited by Selman A. Waksman. (Pp. 412+x; illustrated. 40s.) London: Baillière, Tindall and Cox, Ltd. 1958.

The curve of popularity of a successful antibiotic usually reaches its peak within two years of the drug's introduction, to fall to a steady lower level when its limitations and perhaps its dangers become recognized. That of neomycin is unique in having a quite different shape. Originally commended for the treatment of tuberculosis, neomycin fell into disrepute because prolonged systemic treatment too often results in deafness and renal damage. In the eight years which have followed, other uses for it which obviate this risk have multiplied and there has been a slowly widening recognition of its valuable properties. These are its very broad "spectrum" of activity, its rapid bactericidal action, the fact that bacterial resistance to it rarely develops during treatment, and its apparent lack of sensitizing power. Staphylococci (but usually not streptococci) are as sensitive to it as coliform bacilli, and among the latter even *Proteus*, which often laughs at other broad-spectrum antibiotics, is highly sensitive. Because of its rapid action short periods of systemic treatment involving little risk of toxic effect are often successful, and these may be indicated in septicaemia, pneumonia, and urinary-tract infections. Other uses, involving no such risk, are local. These include oral administration, since little is then absorbed, whether for the treatment of enteritis or for the suppression of the bowel flora before operation, in which neomycin is more successful than any other drug. Application to infected skin and wounds, inhalation and instillation into infected cavities including the peritoneum, have also been successful.

Neomycin has assumed so important a place in therapeutics that an adequate work of reference on it has become a necessity, and this the discoverer himself with three editorial colleagues and no fewer than 32 other contributors have now provided. Earlier sections deal with laboratory aspects, and a final one with miscellaneous matters, including "formulation," uses outside the clinical field, nine pages of a list of proprietary preparations, a three-page list of manufacturers, and a bibliography of 691 items. The clinical sections deal fully with the main uses already mentioned and several others, among them trivialities such as the suppression of axillary odours (is the use of a valuable antibiotic justifiable for this?) and some ingenious prophylactic applications in the urinary tract, including addition to pyelographic contrast media. There is some overlap and repetition among these chapters, particularly in regard to bacterial sensitivities, the effects of oral administration, and the risks of toxic effects. The chapter on urinary-tract infections makes no mention of the vital fact that neomycin is more active in alkaline than in acid media. Those authors who commit themselves seem agreed that systemic treatment with adequate doses in patients with good renal function can safely be given for five to seven days, and there are many situations in which this may be indicated. Clinicians who are not fully aware of the potentialities of this antibiotic except as a skin cream or an intestinal antiseptic will find much valuable information in these pages.

L. P. GARROD.

OPERATIVE SURGERY

Operative Surgery. Edited by Charles Rob, *M.C.*, M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S. Vol. 8. Part XVI: Neurosurgery (pp. 57). Part XVII: Eyes (pp. 83). Part XVIII: Ear, Nose and Throat (pp. 196). (Illustrated. £5 10s.) London: Butterworth and Co. (Publishers) Ltd. 1958.

The last volume of this big work deals with the operative treatment of conditions which affect the central nervous system, the eyes, ears, nose, and throat. The neurosurgery is mostly concerned with those emergency measures which might have to be undertaken as a preliminary to transferring the patient to a special centre, but there are useful accounts of cerebral and cerebellar abscess. In the other sections of the book there are many operations which ought only to be performed by those with special experience; very skilful technique which only specialists gain is needed for corneal grafting, for dealing with a detached retina, and for performing a fenestration operation on the ear. All these operations and many others are well described and illustrated. The ending of a long and arduous task always brings a sense of relief even when the doing of it is to one's liking; we imagine the editors of this system will be relieved that the last volume has now been issued. We congratulate them on the completion of a remarkable and useful work.

ZACHARY COPE.

FUNGUS DISEASES

An Introduction to Medical Mycology. By George M. Lewis, M.D., Mary E. Hopper, M.S., J. Walter Wilson, M.D., and Orda A. Plunkett, Ph.D. Fourth edition. (Pp. 453+xvii; illustrated. £5 15s.) Chicago: Year Book Publishers, Inc. London: Interscience Publishers, Ltd. 1958.

In the earlier editions of this popular work the subject was presented mainly from the viewpoint of the dermatologist. In the new and enlarged fourth edition, however, to which two additional authors have contributed, the great progress in medical mycology during the ten years since the appearance of the third edition is fully reflected and a fairer balance is shown in the respective presentations of the superficial and deep mycoses.

The general plan of the original book has been followed, except that the fungus is now considered with the relevant disease and not in a separate section. The admirable half-tone illustrations, an outstanding feature of the earlier editions, have been increased to 650, in addition to two coloured plates of eight figures and numerous illustrations in the text. However, the new book is not just an atlas of fungus diseases. The chapters dealing with the systemic mycoses have been entirely rewritten and amplified, and this remark applies also to some of the chapters on the dermatophytoses, notably those on infections by *Trichophyton rubrum* and by *T. mentagrophytes* with its variety *T. interdigitale*. The sections dealing with immunology and allergy in superficial and deep mycoses are of particular interest, and the chapters on the fundamentals of elementary mycology and mycological technique, including diagnostic methods and the production of experimental infections in laboratory animals, should prove helpful to the pathologist and the clinician not versed in these matters. A new feature is a short account of fungus diseases in relation to workmen's compensation in the United States. The style is attractive, the descriptions are lucid and concise, and the book offers a simple and adequate introduction to the study of fungus diseases.

J. T. DUNCAN.*

COLLAPSE IN THE OPERATING ROOM

Cardiovascular Collapse in the Operating Room. By Herbert E. Natof and Max S. Sadove, M.D. (Pp. 197+xvi; illustrated. 45s.) London: Pitman Medical Publishing Co. Ltd. 1958.

"Death on the table" is no longer acceptable either as a diagnosis or as the inevitable price of surgery and anaesthesia. Interest has been growing in the varied mechanisms involved in these cases. Particularly does this interest centre on the influence which pre-existing disease may have on the liability to collapse in these circumstances. It is refreshing and most valuable to find the whole subject reviewed in a tidy and sober manner. The authors have studied what is now a very large literature, abstracted its essence, and set down the result against a background of their own experience, which covers 33 cases of "cardiac arrest" in 40,000 operations over a three-year period. It is gratifying that their own views on the prevention and treatment of these accidents conform closely to current

*This review was written shortly before Dr. Duncan's death

practice in Great Britain. Their style is characterized by brevity and by profuse references to literature. Some of the statistical information is presented in cartoon form, in an earnest desire to assist in their assimilation. If the result is not always a happy one, the reader is certain to be tolerant, for the importance of grasping the information is never in doubt. This book is a landmark in this field. It must surely become essential reading for anyone wishing to be knowledgeable about the many and varied aetiological factors which lead to collapse in the operating theatre, and wishing to contribute to the prevention and treatment of these calamities.

W. W. MUSHIN.

ADVANCES IN ALLERGY

Progress in Allergy: Fortschritte der Allergielehre. Volume V. Edited by Paul Kallos. Contributors: St. V. Boyden, L. Brent, M. M. Mayer, O. Ouchterlony, Z. Ovary, W. D. M. Paton, and B. H. Waksman. (Pp. 508+xxxix; illustrated. Sw. fr. 82.) Basel, New York: S. Karger. 1958.

This fifth volume of *Progress in Allergy* follows on similar lines to its predecessors and maintains the same high standards. It comprises a series of articles, each by an outstanding authority, reviewing comprehensively advances in various fields of endeavour all of which contribute to our knowledge of various aspects of the allergic reactions. Advances in the study of the serological properties of different kinds of antibodies and antigens are excellently described and reviewed by Ouchterlony, of Gothenburg, in his article on "Diffusion-in-gel Methods for Immunological Analysis." Boyden, of Copenhagen, also discusses important serological methods such as the Middlebrook–Dubois haemagglutination test and the "coated tanned red cell technique" in his article on the "Immunological Response to Antigens of the Tubercle Bacillus." Z. Ovary, from Johns Hopkins University, reviews the techniques of the sensitive methods developed by himself to demonstrate and measure antigen–antibody interactions in the skin of experimental animals and discusses cutaneous anaphylaxis and the Arthus phenomenon.

Brent, of University College, London, in an article on "Tissue Transplantation Immunity," points out that the grafting of skin has made a special contribution by the unravelling of the immunological factors which are involved. He reviews the evidence in favour of regarding transplantation immunity as related to tuberculin sensitivity and sensitization to simple chemical compounds. Professor Paton, of London, in an excellent article deals with "The Release of Histamine," and points out that to an important extent the physiology of histamine is now the physiology of the granules of the mast cells. In the group of auto-immunological disorders, Waksman, of Harvard Medical School, in an article on "Cell Lysis and Related Phenomena in Hypersensitive Reactions," reviews comprehensively the immunohaematologic diseases. The role of complement is dealt with by M. M. Mayer, of Johns Hopkins University, in his article "Studies on the Mechanism of Hemolysis by Antibody Complement." The introduction by Paul Kallos, the editor, reviews progress in allergy in general and with admirable comments. Each article has a very full list of references, and to all interested in these problems this book can be thoroughly recommended.

D. A. WILLIAMS.

BALLET PHYSIQUE

Ballet Physique, with Notes on Stresses and Injuries. By Celia Sparger, M.C.S.P., C.C.P.E. (Pp. 64; illustrated. 12s. 6d.) London: Adam and Charles Black. 1958.

The question of the relationship between physical form, anatomical structure, and artistic performance is one which has interested many observers, yet no acceptable conclusion has been advanced, and clearly no approach to a generalization can be arrived at unless each art is considered individually, so varied are they. In the case of the painter, for instance, provided he is not colour-blind or paralysed, there is no recognizable physical characteristic; the underlying processes of production are psychological rather than physical. But what of the musical performer—the violinist, the pianist, the guitarist, and others? Here there is obviously a physical element, but it is one which is hampered only by rather gross anatomical defects: absence of a digit, fixity of joints, anaesthesia, and so on. There is no doubt that the essential mechanism is one of cerebral and neural activity producing the marvellous co-ordination of movement demanded for a perfect performance, and of course, behind all, an emotional driving force and determination. The great Paganini is represented in drawings of the time as tall and thin (as indeed he is known to have been), with long arms, thin hands, and fingers that fall well into the medical category of arachnodactyly. His technical abilities were so remarkable that for many years it was accepted that the typical hand and fingers of a great violinist should be long and thin. Yet many virtuosi of comparable technique since that time have hands which are quite podgy and muscular, as indeed might be expected from the constant exercise of the intrinsic hand muscles. Seemingly almost any normal hand would do as the executant mechanism provided the exceptional nervous control was present. It is recorded that one or two outstanding pianists of the last generation actually had the aponeurotic expansions of the extensor tendons of the ring fingers to the third and fifth digits divided to allow of greater individual freedom of movement. That the results were stated to be disappointing is perhaps not surprising, for individuality of finger movement is much more a question of brain and nerve than of tendons. We are thus left with the impression that instrumental virtuosity is generally a matter of nervous control rather than physical form.

The volume under review, however, deals with ballet physique, and in this form of art it is to be expected that physical attributes may be of greater significance. Miss Celia Sparger, from her extensive experience as physiotherapist at the Royal Ballet School, has attempted to find some correlation between physique, form, and performance, and especially to see if there are any characteristics of the young child aspirant which would enable the teacher to judge the future possibilities and thus save the unsuited much wasted effort, disappointment, and frustration. Of course there are definite deformities, such as spinal curvature, unequal limbs, hyperextension of the knees, hallux valgus, and so on, which make further training futile, but the impression we get from the rest of the book is that bodily form from the aesthetic point of view is much more important to success than structure and anatomy, provided that, as in the other arts, the nervous control is perfect. In the author's experience "the physical factor predominates very largely in those who fall by the wayside," and, although we cannot agree entirely with some of the opinions expressed, it would be an audacious reviewer who denied the truth of that statement. Indeed, Miss Sparger realizes how little dogmatism on such a subject is warranted, and we commend the opinion in her preface that "real artistry and the gift of movement will always weigh heavily in the balance against physical imperfections." As a guide to those who teach ballet, for whom it was primarily written, this book has both merit and value.

NORMAN C. LAKE.

A selection of the basic writings of Pavlov (*Experimental Psychology and Other Essays*; 653 pages, illustrated) has been published in Great Britain by Peter Owen, Ltd., price 70s. Included are papers on circulation, digestion, experimental psychology, sleep, hypnosis, and experimental psychopathology.

A collection of life tables and mortality tables have been constructed by R. A. M. Case and Joyce L. Harley, and they are issued under the title *Death Rates by Age and Sex for Tuberculosis and Selected Respiratory Disease, England and Wales 1911–1955* by the Chester Beatty Research Institute, Royal Cancer Hospital, London. Statistics are given for tuberculosis, bronchitis, bronchopneumonia, and lobar and undefined pneumonia.

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TOO SOLID FLESH

Twenty-five years ago obesity was generally held to derive from endocrine causes, known and unknown, so that any obese woman was suspected of Cushing's disease and too many fat boys were referred to consultants with a diagnosis of Fröhlich's syndrome. If an endocrine cause could not be proved—then some metabolic *mystique* was invoked, such as a lowered basal metabolism or some deviation in the individual handling of absorbed nutrients. Such superstitions were strongly attacked by Americans such as L. H. Newburgh,[1] J. W. Conn,[2] and E. H. Rynearson,[3] who easily disposed of these false doctrines and emphasized the basic concept of an intake in excess of output as the cause of simple obesity. Prejudiced advocates of this hypothesis were sometimes even heard to deny that patients with Cushing's syndrome were really fat and the metabolic switch (gluconeogenesis) in this disease was conveniently ignored.

A more fruitful consequence of this rational approach was the inquiry into why some unfortunates eat more than they need. The psychologists investigated the personal and environmental background to obesity; and the animal physiologists made fascinating experiments in mice and rats to illustrate the hypothalamic control of appetite and the mechanism of satiety. It became apparent that the reasons why appetite was not correctly geared to metabolic requirements were exceedingly complicated in small animals and might well be not less complex in man. Simple obesity seemed to be not so simple after all.

At this time it was customary to deny the importance of daily activity in the prevention of obesity. Perhaps this was to be expected of a generation which had forgotten how to walk but had learnt to hike. And as for infrequent outbursts of violent exercise, it was said that the 300 calories expended in half an hour's squash rackets were replaced by two dry Martinis. These opinions ignored earlier evidence[4] that when activity is reduced appetite is sustained and weight is consequently increased. Meanwhile the statistics of the insurance companies showed that obesity constituted a hazard to both health and longevity; physicians and family doctors in their clinics and consulting rooms referred fat patients to dietitians or gave them printed diet-sheets accompanied by perfunctory warnings. The remission rate among those treated thus was moderately good but the relapse rate was high; and the weak-willed were assisted by an effective depressant of appetite—dexamphetamine. Food manufacturers, magazine-writers, the pharmaceutical industry, and the nutritionists introduced a great variety of slimming diets, and many books have also been written for the greedy public. All the diets advised, however described and no matter how much their minor differences are emphasized, are alike in prescribing a low intake of calories and carbohydrates.

There are signs that we are emerging from this period of clamour and confusion. There is an increasing awareness that what is now needed is the patient collection of more facts both by clinicians and by physiologists, not only to elucidate the deviations of the central and peripheral mechanism at work but also in order to correct these in the individual patient. J. Mayer[5] and H. Bruch[6] have recently published useful reviews of American work in this field, and it may not be chauvinist, even at Christmas-time, to point out that there has been much distinguished British work that they do not mention. Investigators here have been interested in the possibility that abnormal metabolic mechanisms were operating, whether primarily or secondarily disturbed. D. M. Lyon, D. M. Dunlop, and C. P. Stewart,[7] by estimating respiratory quotients, showed that in undernourished obese subjects fat was converted into carbohydrate. A. Kekwick and G. L. S. Pawan[8] have given patients iso-caloric diets containing varying quantities of protein, fat, and carbohydrate and shown that their loss of weight was most rapid when on a high fat intake and least rapid with high-carbohydrate diets. They concluded that the weight loss on the high-fat regime could not be entirely accounted for by loss of water, though R. Passmore, J. A. Strong, and F. J. Ritchie[9] have shown that as much as 2–4 litres of body water may be lost in the first week when patients were put on diets with energy deficits of 2,500–3,000 calories. T. M. Chalmers and colleagues[10] have detected a "fat-mobilizing substance" in the urine of obese patients given a diet of 90% fat or protein, but it disappears on a diet

[1] Newburgh, L. H., *Physiol. Rev.*, 1944, **24**, 18.
[2] Conn, J. W., ibid., 1944, **24**, 31.
[3] Rynearson, E. H., *Proc. roy. Soc. Med.*, 1951, **44**, 951.
[4] Bruch, H., *Amer. J. Dis. Child.*, 1940, **60**, 1082.
[5] Mayer, J., *Borden's Rev. Nutr. Res.*, 1958, **19**, 3.
[6] Bruch, H., ibid., 1958, **19**, 4.
[7] Lyon, D. M., Dunlop, D. M., and Stewart, C. P., *Biochem. J.*, 1932, **26**, 1107.
[8] Kekwick, A., and Pawan, G. L. S., *Lancet*, 1956, **2**, 155.
[9] Passmore, R., Strong, J. A., and Ritchie, F. J., *Brit. J. Nutr.*, 1958, **12**, 113.
[10] Chalmers, T. M., Kekwick, A., Pawan, G. L. S., and Smith, I., *Lancet*, 1958, **1**, 866.
[11] Booyens, J., and McCance, R. A., ibid., 1957, **1**, 225.
[12] Dodds, E. C., *Proc. roy. Soc. Med.*, 1950, **43**, 342.
[13] Strong, J. A., Passmore, R., and Ritchie, F. J., *Brit. J. Nutr.*, 1958, **12**, 105.
[14] Sheldon, J. H., *Lancet*, 1949, **2**, 869.
[15] Wolff, O. H., *Quart. J. Med.*, 1955, **24**, 109.
[16] Mullins, A. G., *Arch. Dis. Childh.*, 1958, **33**, 307.
[17] *Boswell's Life of Johnson*, 1904, vol. 2, p. 491, Henry Frowde, London.

of 90% carbohydrate. This "substance" may be concerned in the observations of Lyon and colleagues made 25 years ago.[7]

J. Booyens and R. A. McCance[11] have recently investigated the basal metabolic rates of 36 normal subjects and reported that three of them had rates which were 30% below the average for the group. None of these three persons was overweight, so their appetite centres had apparently no difficulty in gearing their food intake to their low metabolic turnover. Can the B.M.R. be put into top gear to allow for the maintenance of a stable weight despite forced feeding? E. C. Dodds[12] reported that it can, but this observation has not yet been confirmed.

Other workers have been interested in the effect of exercise on obesity. J. A. Strong and colleagues[13] point out that, while it is true that one hour's walking each day will expend only 350 calories, yet three hours' daily walking for a month will utilize 9 lb. (4 kg.) of fat. They persuaded their obese patients to take this exercise on a daily diet of 400 calories, with consequent weight losses up to a maximum of 35 lb. (16 kg.) in six weeks. Contributing to the natural history of the disease, J. H. Sheldon[14] has described the obesity of pregnancy and the puerperium—maternal obesity; O. H. Wolff[15] has shown that the increased height of obese children, and their early puberty, are the result of a food intake in excess of their requirement; and A. G. Mullins[16] reported recently that one-third of the obese adults in an out-patient clinic were cases of persistent juvenile obesity, and that the failure in this group to reduce weight was associated with psychological factors, in particular low intelligence. Children of low intelligence are not only less active mentally but also more inert physically than their brighter brethren.

There is in some recent literature a disposition to decry the importance of attempting to reduce weight by dietetic restriction. In so far as this emphasizes the importance of increased exercise one can heartily agree with it; and when it represents the need for a more careful consideration of the patient's history, constitution, personality, and environment, it is a healthy reaction from the diet-sheet-over-the-counter policy. Diets must be low both in calories and in carbohydrate; they can be sufficiently high in protein to provide for the nitrogen needs of adults, and also of growing children. Ketosis does not matter, and high-fat diets may assist weight reduction.

But when all is said and done the modern nutritionist has done little more than dot the "i's" and cross the "t's" of the following robust conclusion of Dr. Samuel Johnson[17]:

> "Talking of a man who was grown very fat, so as to be incommoded with corpulency, he said, 'He eats too much, Sir.' BOSWELL: 'I don't know, Sir; you will see one man fat who eats moderately, and another lean who eats a great deal.' JOHNSON: 'Nay, Sir, whatever may be the quantity that a man eats, it is plain that if he is too fat, he has eaten more than he should have done. One man may have a digestion that consumes food better than common; but it is certain that solidity is increased by putting something to it.' BOSWELL: 'But may not solids swell and be distended?' JOHNSON: 'Yes, Sir, they may swell and be distended; but that is not fat.'"

DEFECTS IN STERILIZATION

Hospital infection is now causing more concern than at any time since before Lister. Two recent contributions to the subject are therefore timely. The first is the publication of a report by the Nuffield Provincial Hospitals Trust,[1] the second is the holding of a conference by the South-west Metropolitan Regional Hospital Board at Southampton last week which is reported in the *Journal* at p. 1589.

How far is the spread of infection in hospitals due to major faults in aseptic technique, and in particular to failure in processes of sterilization? Those who would answer that such elementary faults must be highly exceptional and can have little to do with the present state of affairs may be compelled to revise their ideas when they read the new report.[1] It is an instructive and disturbing document which deserves the closest attention from all engaged in any way in the practice of surgery. This is only an interim report. An operational research team which had completed a report[2,3] on the organization of central syringe services was instructed to study the organization of central supply departments for all sterile materials. The first question to be answered was whether such departments are necessary, and this entailed a study of present sterilizing practice. The results of this were so disquieting that it was decided to publish them at once.

The six hospitals studied were a London teaching hospital, three in provincial cities, and two cottage hospitals. They are not named, and it is not clear how they were chosen, but they are said to be representative. The first part of the report deals with ward practice, and criticizes many features of "utility rooms." These were found to be liable to contamination from open windows, from excessive traffic through them (one contained the ward

[1] *Present Sterilizing Practice in Six Hospitals*, 1958, Nuffield Provincial Hospitals Trust, Nuffield Lodge, Regent's Park, London, N.W.1, price 5s.
[2] *The Planning and Organization of Central Syringe Services*, 1957, Nuffield Provincial Hospitals Trust, London.
[3] *Brit. med. J.*, 1958, **1**, 93.
[4] Bowie, J. H., *Pharm. J.*, 1955, **174**, 473 and 489.
[5] *Brit. med. J.*, 1955, **1**, 350.
[6] Howie, J. W., and Timbury, M. C., *Lancet*, 1956, **2**, 669.

telephone), and from the disposal of soiled dressings. Many sterilizers were unsatisfactory in various ways, particularly in not being fitted with a rheostat, and excessive scaling was observed in them and on utensils boiled in them. Nine different disinfectant solutions were found to be in use for storing instruments or for actually sterilizing them; in this and other matters practice varied from ward to ward in the same hospital as well as in different hospitals, to the detriment of nurses' training. Arrangements for treating soiled linen are strongly criticized: nurses are expected not only to disinfect this but to dry it before dispatch to the laundry, and this entails hanging up large numbers of wet sheets in sluice- and bath-rooms.

Bed-pan washing was unsatisfactory; 64 out of 166 examined still contained faecal material. Dressing drums were often battered and so damaged, as by actual perforation or ill-fitting lids, that their contents were directly exposed to contamination. They were often too tightly packed or lined with unsatisfactory material or (in 46 out of 150 examined) not lined at all. After autoclaving they were not always labelled as sterilized. One way mentioned of distinguishing between sterile and unsterile drums on the same trolley was "to feel them to see which were warm." When syringes were sent for autoclaving they were often packed in drums or other metal receptacles (a cake tin and old tulle-gras tins are mentioned) or in tubes tightly plugged and even sealed with adhesive tape, so that penetration by steam, particularly of an assembled and lubricated syringe, could never have taken place. There are many photographs of such defective apparatus and of ward scenes illustrating these difficulties and dangers. A notable and regrettable omission is that of any reference to methods of sterilizing apparatus used for lumbar puncture, for this is the most dangerous of all ward procedures when sterility is in any doubt, and a central supply service can perform perhaps its most vital function in catering properly for it.

Operating-theatres are only briefly considered. Some structural and ventilating defects are mentioned, and the report also criticizes inadequate washing of walls and the laying out of sterile equipment on trolleys too long before it is to be used. In one theatre "the staff had to wage continual war on cockroaches," and in one autoclave room drums were contaminated by bird droppings from a ventilator—these are picturesque but evidently exceptional features. It is also probably exceptional for new scalpel blades to be "sterilized" chemically without removal of their protective grease. Criticism is concentrated in this part of the report not on the theatres but on the autoclaves. Those familiar with the relevations of J. H. Bowie[4,5] and of J. W. Howie and M. C. Timbury[6] are aware that antiquated autoclaves are still in use, the satisfactory operation of which is either impossible or unduly time-consuming or damaging. Only one of the 25 autoclaves tested here was found defective from "mechanical inefficiency and old age"; for eight others classed as inefficient, five of which failed either to convert the colour of Browne's tubes or to kill test spores, faulty installation or, more commonly, faulty operation was responsible. In three instances the chamber drain through which air must be discharged was kept closed throughout the run. Air filtration was unsatisfactory in four instances, and the fact that no less than 38% of swabs from the interior of drums yielded bacterial growth is attributed largely to recontamination during the drying stage. These were only some of many cultures made from supposedly sterile materials in wards and theatres: of the total, 17% were unsterile.

The report finally makes recommendations for the immediate improvement of sterilizing practice without any great extra cost. Ward practices should be standardized, syringes sterilized centrally, and reform introduced in the disposal of soiled dressings (paper bags are preferred) and dirty linen. The report considers that drums should be abolished and replaced by cardboard boxes. These are exactly specified and have been shown to be well penetrated by steam and yet to protect their contents from subsequent contamination. No doubt drums must go, but consideration might have been given to another alternative, universally employed in the United States—that of wrapping in a double layer of fabric. Material like cardboard is loaded with spores of *Clostridia*—as indeed has been confirmed by cultivating the material of these boxes—and, though the manufacturer promises pre-sterilization and they ought in any case to be sterilized in use, such material may seem out of place in an operating theatre. The most important recommendations concern the operation of autoclaves and the defining of responsibility for supervision, particularly of this operation, and of other tasks as well. Autoclave attendants, whose standards of aseptic discipline are severely criticized apart from their actual operation of their machines, were variously under the impression that they were responsible to the head porter, the theatre sister, the secretary, or the engineer. One "was inclined to feel that he owed allegiance to the matron, but this was mainly because he also drove the nurses' bus." It is abundantly clear that this vital task should be in the hands of a man who understands it, which means training and upgrading, and he should evidently be responsible to someone—

according to this report the bacteriologist—who should also conduct monthly tests of working efficiency.

Hospitals throughout the country will do well to inquire whether the graver shortcomings described here exist in their own practice. It is surely an elementary requirement in the campaign against hospital infection that materials supposed to have been sterilized by heat should in fact be sterile and remain so. In some other matters, particularly of ward technique and where chemical disinfectants are concerned, it still seems necessary to define optimum methods. What is at present largely left to the ward or theatre sister could benefit by attention from both bacteriologist and surgeon.

ONE HUNDRED YEARS OF CELLULAR PATHOLOGY

The doctrine of cellular pathology as first expounded by Virchow in his epoch-making book[1] published 100 years ago focused attention on the histology of diseased organs. It replaced the outworn ideas of humoral pathology by the conception of pathological changes occurring within the individual constituent cells of an organ. A natural consequence of the famous maxim *omnis cellula e cellula* was that the origin of disease must henceforth be sought in hitherto unexplored territory to be revealed by the microscope. The familiar gross morbid changes of a diseased organ were now proclaimed to be only the visible manifestation of reactions taking place at the microscope level of histopathology. Speaking of the influence of Virchow's teaching on contemporary thought, Lord Lister once said that it "had swept away the false and barren theory of a structureless blastema, and established the true and fertile doctrine that every morbid structure consists of cells which have been derived from pre-existing cells as a progeny. . . . Even those morbid structures which deviate most from the normal structure are known to be derived as a progeny from normal tissue—from normal cells, driven to abnormal development by injurious agencies."

The general effect of Virchow's teaching was to lessen the importance of "humoral" pathology and greatly increase the importance of "cellular" pathology, and it was many years before advances in immunology and endocrinology began to readjust the balance. The many different varieties of "humoral" antibody which we now know to be of such importance in relation to the process of immunity were undiscovered when Virchow first propounded the doctrine of cellular pathology.

Yet though he took his stand almost exclusively on the basis of pathological anatomy he did not minimize the importance of pathological physiology, and the logical development of Virchow's cellular pathology has resulted in great advances both in pathological anatomy and in pathological physiology. This is shown conclusively by the series of articles contributed to the current number[2] of the *Journal of Clinical Pathology*, which commemorates the centenary of Virchow's *Cellular Pathology*. The first article, by Sir Roy Cameron, is a richly illustrated historical review of the mid-nineteenth century period and the setting in which Virchow lived. Then follow a series of articles on subjects which may be described as natural developments of the doctrine of cellular pathology. Of special interest is the review of modern concepts of cellular structure by Professor Robert Cruickshank and the authoritative account by Dr. Honor Fell of the astonishing developments in the field of tissue culture.

Another natural development of cellular pathology has been the concept of the cell as a complete nutritional as well as a structural unit. This becomes clear from Dr. J. W. Harman's stimulating article on the cytochondrial aspects of cellular pathology. It is as if a vast panorama of subcellular structure and function has been opened up, permitting advance "beyond the cellular into the subcellular range of disease." One other paper in this special number of the *Journal of Clinical Pathology* deserves special mention, that by Dr. A. G. Everson Pearse entitled "Extension of the Limits of Cellular Pathology—the Role of Enzyme Histochemistry." This shows how, by the application of new histological techniques, the limits of cellular pathology drawn up by Virchow 100 years ago have been pushed forward in precisely the way he foretold. In particular the newer techniques of functional histochemistry have begun to transform descriptive analytical histopathology into a new science of functional cytopathology.

One of the results of recent developments in the field of enzyme histochemistry has been to show how misleading it may be to regard tissues as homogeneous. It seems now as if histologically identical cells may have entirely different enzymic composition. Looking forward into the future Dr. Pearse thinks that a further application of the new techniques he has described may be expected in the field of experimental pharmacology "where it may be possible to demonstrate the earliest effects of drugs

[1] Virchow, R. L. K., *Die Cellularpathologie in ihrer Begründung auf physiologische und pathologishe Gewebelehre*, 1858, Berlin.
[2] *J. clin. Path.*, 1958, **11**, No. 6.

upon cells in section, smears, or tissue cultures, with obvious economy of effort." Dr. Pearse concludes by wishing that Rudolf Virchow were here to-day to describe for himself the possibilities for even further extensions of the science of pathology as it seems to be opening up before us to-day. Cellular pathology has become an "expanding universe."

YAWNING

J. Barbizet has done a useful service in reminding us how little is known about the everyday occurrence of yawning. In a short article[1] he concisely and clearly covers almost all that can be said about it from the physiological, psychological, and clinical points of view. The act of yawning is involuntary and unfolds itself in a fairly consistent way, beginning with an active inspiratory movement that is chiefly remarkable for the enormous dilatation of the pharynx. At the height of the inspiration there are associated facial movements and then very often generalized stretching of the limbs. This is followed by the third phase of passive expiration. Such movements are seen also in many animals, and there is possibly a connexion between it and, for example, certain movements of birds' beaks accompanied by the flapping of wings.

Drowsiness and boredom are the usual precipitating causes of yawning. It has been observed in some neurophysiological experiments but usually in association with sleep. No "centre" for yawning has been detected by direct stimulation, nor have the conditions been defined that will invariably produce it. Barbizet considers it likely to be related to the activity of the brain-stem reticular formation, whose function is intimately related to the level of wakefulness of the brain. In support of this is the fact that yawning is commonly observed in association with lesions of the brain-stem or lesions indirectly compressing it. It is among the sequelae of encephalitis lethargica, and is occasionally seen as an aura of epilepsy. However, A. P. Heusner[2] cites various authors who describe the complex yawning–stretching act in anencephalic infants, which would put the controlling centre, if it exists, at the level of the lowest centre of respiration.

The possible functional significance of yawning is unsettled. The movement may increase venous circulation to the heart, and as a result of increased cardiac output the brain might benefit, but direct observations of the effect of yawning on the cerebral circulation are missing. Heusner finds a systemic vasoconstriction and transient tachycardia, probably the same as that obtained by any deep inspiration.[3]

In many ways the most interesting and tantalizing aspect of yawning is its relation to psychological factors and in particular the way in which it seems to be infectious in a group. The act is part of the complex language of gesture that long preceded speech as a means of communication in the prehistory of man, a subject greatly enlarged by the work of ethologists such as Lorenz and Tinbergen. In some unknown way animals are tuned to respond to significant signals of their own species. Yawning is a relatively simple signal, and the perception of its social meaning—boredom, presumably—may hardly require any learning by environmental experience. We seem to know more about the social significance of yawning than the part, if any, it plays in the homoeostasis of the body.

[1] Barbizet, J., *J. Neurol. Neurosurg. Psychiat.*, 1958, **21**, 203.
[2] Heusner, A. P., *Physiol. Rev.*, 1946, **26**, 156.
[3] Bolton, B., Carmichael, E. A., and Sturup, G., *J. Physiol.* (*Lond.*), 1936, **86**, 83.

BLOOD SUGAR IN CYCLIC VOMITING

Cyclic or recurrent vomiting or the "periodic syndrome" has been recognized for a long time as one of the more common psychosomatic disorders of childhood. Its exact pathogenesis has not yet been determined, but it is known to be prevalent among only children, usually of highly strung temperament and above average mentality, and to be related possibly to migraine in later life. It has also been held, in a few cases, to be a manifestation of epilepsy, on the grounds that abnormalities in the E.E.G. are not infrequent and that phenytoin in such cases is the most successful therapeutic agent.[1]

A number of biochemical studies have been undertaken, particularly of the ketosis, but the findings have varied. Blood-sugar estimations and glucose-tolerance curves have also produced conflicting results; for, though there is general agreement that the glucose-tolerance curve is within normal limits, some authors have reported hypoglycaemia and others hyperglycaemia. These differences may well be related to the phase of the attack in which the estimation is made. The general statement in most textbooks is that cyclic vomiting is associated with hypoglycaemia, and the importance of this is evident in the differential diagnosis between cyclic vomiting and diabetic coma. W. W. Payne, however, in 1951[2] reported raised blood sugars in his patients, and more recently L. Salomensen and K. Harnaes[3] have supported him. They quote a number of Scandinavian authors who have found hyperglycaemia at the onset of the attack and add two cases of their own in which the levels of blood sugar were 400 and 276 mg. per 100 ml. respectively on the second day of the attack.

As the condition is usually benign and readily recognized in any child after the cycle has been established it might be thought that discussions about blood-sugar levels were more academic than practical, but, because of the differential diagnosis, it is important to ensure that nothing has been overlooked. Apart from diabetic coma, which may indeed be the first indication of diabetes in a child, appendicitis and cerebral tumour are two other conditions which may present similarly—both conditions which require urgent diagnosis. A good physical examination will go further, and more quickly, in excluding the more serious conditions, and the family doctor is wise if, at the onset of each recurrence, he just makes sure that it is running true to form.

[1] Livingston, S., *Advanc. Ped.*, 1958, **10**, 137.
[2] Payne, W. W., *Proc. roy. Soc. Med.*, 1951, **44**, 724.
[3] Salomensen, L., and Harnaes, K., *Acta Paediat.* (*Uppsala*), 1958, **47**, 383.

TABLET TREATMENT OF DIABETES

Two recent reports,[1] [2] one from Germany and the other from Switzerland, review recent results with sulphonylurea derivatives in the treatment of diabetes. While presenting no new facts, these reports on the treatment of large numbers of diabetics over long periods help to confirm the opinions that have already been formed about existing oral antidiabetic drugs.[3] Practically everywhere the original BZ 55 (carbutamide) has been replaced by D 860 (tolbutamide). Few side-effects after tolbutamide have been recorded, although the effective dose in grammes or tablets is slightly more than that of carbutamide. Among the older patients, mainly but not entirely in the category of obese, success in controlling glycosuria has been achieved in 80% or more. In contrast, there have been hardly any successes in younger patients (even up to the age of 40), and all the Continental writers agree that any patient on 40 units or more of insulin will not respond to treatment with tolbutamide. This confirms world-wide experience. Clinical symptoms of hypoglycaemia are rare, but one fatal case is reported.[3] German physicians now agree that strict dieting is necessary to control glycosuria during tablet treatment, and that patients taking tolbutamide tend to exert less self-discipline in restricting themselves to a diet than those taking insulin. As to the pharmacological action of tolbutamide, the Continental reports mostly concentrate on the theory that the beta cells of the pancreas are stimulated to secrete more insulin, which explains the failure of the tablets in severe diabetes and depancreatized animals.

HAZARDS OF MEPROBAMATE

Meprobamate ("equanil," "mepavlon," "miltown") was a late comer among the tranquillizers and has until recently been regarded as relatively innocuous compared with chlorpromazine and reserpine. Observations reported over the last few months indicate that this view can no longer be held; indeed, reports show that it can do serious harm. The drug has been shown to cause habituation,[4] with a typical withdrawal syndrome including insomnia, vomiting, tremors, muscle twitching, anxiety, anorexia, ataxia, and, less frequently, hallucinations. In three out of four patients with the withdrawal syndrome grand-mal seizures developed. The risk of addiction was found to be especially serious in patients with a history of alcohol and other addictions.[5] These observations are not invalidated by the outcome of a double-blind trial[6] in which a group of elderly people failed to show withdrawal symptoms following eight weeks' administration of meprobamate. Evidence of the drug's toxicity has also been growing, and fatalities have been observed. Acute meprobamate poisoning is apt to produce stupor and coma up to complete respiratory and circulatory collapse. The usual analeptics proved effective antidotes in most cases. An average of one in 200 patients is believed to show an idiosyncrasy to the drug.[7] Its manifestations are urticaria, vomiting, fever, oedema, arthralgia, petechiae, bronchospasm, and headaches. Meprobamate has no longer a clean record with regard to suicide. L. W. Powell and his associates[8] reported two cases of suicide following the ingestion of 12 g. and 20 g. respectively. Suicidal attempts with this drug have been observed not infrequently. Finally, a fatal case of aplastic anaemia due to meprobamate therapy has recently been recorded.[9]

It is not surprising that these reports come from the United States, where this drug has had a tremendous vogue, and they are worth bearing in mind over here. W. Sargant[10] and others have found the drug of only limited value in the treatment of the neuroses compared with the much cheaper barbiturates, and there would seem to be rather few types of case in which benefit may be expected from it.

MEDICAL BENEVOLENCE

The advantage to be gained by subscribing to a charity under covenant is now well known: if a promise is made to make a payment for seven consecutive years recovery of income tax is then allowed at the standard rate on each payment, bringing substantial benefit to the charity without extra cost to the subscriber. The Charities Trust Fund of the B.M.A. has recently been recognized as a charity, and earlier this month the Chairman of Council, the Treasurer, and the Chairman of the Charities Committee urged members to give much-needed help to the medical charities by undertaking a covenant (*Journal*, December 6, p. 1410). They pointed out that appeals from aged and sick members of the profession and from widows and orphans are greater than ever, and because of the fall in the value of money the need keeps increasing. Those who do not already contribute independently, by covenant or otherwise, to individual charities will find on the form of application for the renewal of their subscription to the B.M.A. a "box" for indicating that they would like to undertake a covenant. The necessary forms will then be sent to them for completion. The fact that the renewal of subscription form comes at a time when there are many other demands for cash should not deter doctors from deciding to contribute to medical charities. In fact the New Year is an especially appropriate time to come to such a resolve. Particulars of individual charities are given on the back of the application form for the B.M.A. subscription. Each one attempts to fill a serious want, but those members who have no particular preference will find the B.M.A. Charities Trust Fund a very suitable object to support. As Dr. Wand and his colleagues explained in their letter: "The B.M.A. Charities Committee is a collecting body which advises the Council on the best method of distributing to other charities the money it collects in the Charities Trust Fund."

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[1] *Dtsch. med. Wschr.*, 1958, **83**, 1253–1268.
[2] Hofstetter, J. R., and Ramel, Ch., *Schweiz. med. Wschr.*, 1958, **88**, 821.
[3] See leading article in *Brit. med. J.*, 1957, **2**, 343.
[4] Halzlip, M., and Ewing, A., *New Engl. J. Med.*, 1958, **258**, 1181.
[5] Mohr, C., and Mead, B. T., ibid., 1958, **259**, 865.
[6] Boyd, L. J., Cammer, L., Mulinos, M. G., Huppert, V. F., and Hammer, H., *J. Amer. med. Ass.*, 1958, **168**, 1839.
[7] Charkes, N. D., *Arch. intern. Med.*, 1958, **102**, 584.
[8] Powell, L. W., Mann, G. T., and Kaye, S., *New Engl. J. Med.*, 1958, **259**, 716.
[9] Meyer, L. M., Heeve, W. L., and Bertscher R. W., ibid., 1957, **256**, 1232.
[10] Sargant, W., *Brit. med. J.*, 1958, **2**, 1095.

NOAH—AN ALBINO

BY

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Noah, with his wine, his ark, and the animals that came two by two, is probably the first vividly human figure in the Biblical account of the early days of man. In this he differs from the weak and gullible Adam, the milksop Abel, the stage villain Cain, and Methuselah, whose main distinction was not to have died young. Amongst Noah's shadowy progenitors his father, Lamech, has persisted as little more than a name. The birth of Noah is recorded in Genesis briefly, with an indication that he was called to a high mission[1]: "And Lamech lived an hundred eighty and two years, and begat a son: And he called his name Noah, saying, This *same* shall comfort us concerning our work and toil of our hands, because of the ground which the Lord hath cursed." The subsequent account of the Flood and the emergence of Noah as the first boat-builder and sailor in the world's history reveals the nature of the mission to which he was born.

Enoch's Record of the Birth of Noah

A fuller account of the birth of Noah is contained in the Book of Enoch the Prophet, one of the more significant volumes in the Pseudoepigrapha.[2] It appears to have been written in the second and first centuries B.C., and greatly influenced the writers of the New Testament, in which it is quoted by name in several passages. Possessing at first the weight of a canonical book, it gradually declined in importance and finally fell under a ban of the Church. It does not appear to have received much attention after the ninth century, and came to be regarded as lost till three manuscripts in Ethiopian were brought from Abyssinia by Bruce in 1773. The Book of Enoch, like the rest of the Apocalyptic literature, is heavy with primitive mythological and cosmological traditions. It relates in considerable detail of "the Watchers of heaven, who have deserted the lofty sky, and their holy everlasting station, who have been polluted with women.[3] . . . And the women conceiving brought forth giants."[4] The birth of Noah is recorded in similar mystical terms.[5]

After a time, my son Mathusala took a wife for his son Lamech.

She became pregnant by him, and brought forth a child, the flesh of which was white as snow, and red as a rose; the hair of whose head was white like wool, and long; and whose eyes were beautiful. When he opened them, he illuminated all the house, like the sun; the whole house abounded with light.

And when he was taken from the hand of the midwife, opening also his mouth, he spoke to the Lord of righteousness. Then Lamech his father was afraid of him; and flying away came to his own father Mathusala, and said: I have begotten a son, unlike to other children. He is not human; but, resembling the offspring of the angels of heaven, is of a different nature from ours, being altogether unlike to us.

His eyes are bright as the rays of the sun; his countenance glorious, and he looks not as if he belonged to me, but to the angels.

I am afraid, lest something miraculous should take place on earth in his days.

And now, my father, let me entreat and request you to go to our progenitor Enoch, and to learn from him the truth; for his residence is with the angels.

When Mathusala heard the words of his son, he came to me at the extremities of the earth; for he had been informed that I was there: and he cried out.

I heard his voice, and went to him, saying; Behold I am here, my son; since thou art come to me.

He answered and said; On account of a great event have I come to thee; and on account of a sight difficult to be comprehended have I approached thee.

And now, my father, hear me; for to my son Lamech a child has been born, who resembles not him; and whose nature is not like the nature of man. His colour is whiter than snow; he is redder than the rose; the hair of his head is whiter than white wool; his eyes are like the rays of the sun; and when he opened them he illuminated the whole house.

When also he was taken from the hand of the midwife, he opened his mouth, and blessed the Lord of heaven.

His father Lamech feared, and fled to me, believing not that the child belonged to him, but that he resembled the angels of heaven. And behold I am come to thee, that thou mightest point out to me the truth.

Then I, Enoch, answered and said; The Lord will effect a new thing upon the earth. This have I explained, and seen in a vision. I have shown thee that in the generations of Jared my father, those who were from heaven disregarded the word of the Lord. Behold they committed crimes; laid aside their class, and intermingled with women. With them also they transgressed; married with them, and begot children.

A great destruction therefore shall come upon all the earth; a deluge, a great destruction, shall take place in one year.

This child which is born to you shall survive on the earth, and his three sons shall be saved with him. When all mankind who are on earth shall die, he shall be safe.

And his posterity shall beget on the earth giants, not spiritual, but carnal. Upon the earth shall a great punishment be inflicted, and it shall be washed from all corruption. Now therefore inform thy son Lamech, that he who is born is his child in truth; and he shall call his name Noah, for he shall be to you a survivor. He and his children shall be saved from the corruption which shall take place in the world; from all the sin and from all the iniquity which shall be consummated on earth in his days. Afterwards shall greater impiety take place than that which had been before consummated on the earth; for I am acquainted with holy mysteries, which the Lord himself has discovered and explained to me; and which I have read in the tablets of heaven.

In them I saw it written, that generation after generation shall transgress, until a righteous race shall arise; until transgression and crime perish from off the earth; until all goodness come upon it.

And now, my son, go, tell thy son Lamech,

That the child which is born is his child in truth; and that there is no deception.

When Mathusala heard the word of his father Enoch, who had shewn him every secret thing, he returned with understanding, and called the name of the child Noah; because he was to console the earth on account of all its destruction.

The version in Genesis, and that in the Book of Enoch, are thus supplementary. Both stress that Noah was born to a dedicated life, as is testified by his name, which is derived from the Hebrew verb signifying to comfort. The Book of Enoch, with its emphasis on his unusual appearance at birth, merely builds up a supernatural background to a worldly mission.

A Reconstructed Fragment

A totally different possibility is suggested by the deciphered fragment of Column II of a particularly badly preserved scroll from the Dead Sea caves (Qumran I), brilliantly identified by N. Avigad and Y. Yadin as a Genesis Apocryphon, and not the lost Book of Lamech as was first supposed. Their reconstruction of this fragment shows Lamech's preoccupation with his wife's faithfulness—a reaction noted repeatedly all through the ages in the literature on the birth of abnormal children to normal parents. It is only when Lamech is assured by his wife with considerable verbal emphasis that the unusual child is indeed his that he hastens to his father, Methuselah, and his grandfather, Enoch (who sojourns with the angels), to obtain a more complete explanation of an exceptional event.[6]

1. Then I thought in my heart that the conception had been from the Watchers and the . . . from the holy ones or [?] the fallen angels.

2. And my heart was changed because of this child.

3. Then I, Lamech, was frightened and I came to BT'NWŠ, my wife, and [I said] . . .

4. "[. . . Swear to me] by the Most High, the Lord of greatness, King of all worlds . . . . .

5. . . . . Sons of Heaven till thou tellest me all in truth if . . . . .

6. [In truth ?] Tell me without lies . . . . . .

7. By the King of all worlds till thou speakest with me in truth and with no lies" . . . . .

8. Then BT'NWŠ, my wife, spoke to me with vigour and with . . . . .

9. And she said, "O my brother and O my lord, remember my pleasure . . . . .

10. . . . . the period, and my spirit into the midst of its sheath and I in truth all . . . . ."

11. . . . . And my heart then had changed within me greatly.

12. When BT'NWŠ, my wife, perceived that my countenance had changed . . .

13. Then she suppressed her wrath and spoke to me and said, "O my lord and O my [brother] . . . . .

14. My pleasure, I swear to thee by the great Holy One, the King of H[eaven ?] . . .

15. that thine is this seed and from thee is this conception and from thee was the fruit formed . . . . .

16. And it is no stranger's, nor is it of any of the Watchers or of the Sons of Heaven . . . [What]

17. has so altered and blemished thy countenance and [why] is thy spirit so low ? . . .

18. In truth I speak with thee."

19. Then I, Lamech, hastened to Methuselah, my father, and I [told him] all . . .

20. his father and he would of a surety learn all from him, for he was the beloved and [. . . with angels]

21. his lot was apportioned and to him they tell all. And when Methuselah heard . . .

22. . . . . to Enoch, his father, to learn all in truth from him.

23. his will. And he went to . . . . . and found him there . . .

24. And he said to Enoch, his father, "O my father and O my lord, to whom I . . . . .

25. . . . And I shall tell thee that thou shouldst not be angered that I have come hither . . . . . .

26. Fear . . . . . .

In the light of this fragment the account of Noah's appearance at birth, as given in the Book of Enoch, is clearly not that of a miraculous child but of an albino. A body white as snow, hair white as wool, and eyes that are like the rays of the sun—these are the unequivocal physical features to be considered once the laudatory commendations are disregarded.

Origin of Noah's Albinism

The fragment also allows some conclusions on the mode of inheritance of Noah's albinism. On the strength of line 9, and their reconstruction of the last word in line 13, Avigad and Yadin hold that BT'NWS, Lamech's wife, was also his sister. If this were so—and such relationship was not particularly unusual in primitive societies—Noah becomes the offspring of an extreme type of consanguineous marriage, and his albinism would illustrate not only the antiquity of the affection, but also the fact that the first recorded case showed parental consanguinity. On this reading, Methuselah can now claim the additional distinction of being the first authenticated carrier of albinism—unless the distinction belongs to his anonymous wife (Fig. 1). Avigad and Yadin, however, point out that their reading is contradicted by the one other extant reference to Lamech's wife.[7] The Book of Jubilees, iv, 28, refers to her as "Betenos the daughter of Baraki'il, the daughter of his [Lamech's] father's brother (or father's sister)." This would seem to show Lamech and his wife as first cousins—the common type of consanguinity in albinism—and would exclude Methuselah's wife as a carrier (Fig. 2). On either reading the consanguineous origin of Noah's albinism is beyond question. BT'NWS and Lamech not only produced Noah but also made genetic history. They deserve better than the oblivion that shrouds them.

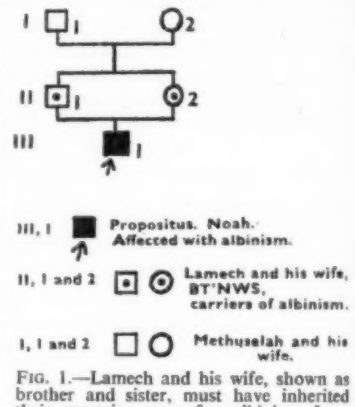
I
II
III
III, 1 Propositus. Noah. Affected with albinism.
II, 1 and 2 Lamech and his wife, BT'NWS, carriers of albinism.
I, 1 and 2 Methuselah and his wife.

FIG. 1.—Lamech and his wife, shown as brother and sister, must have inherited their recessive gene for albinism from either their father, Methuselah (I, 1), or their mother (I, 2).

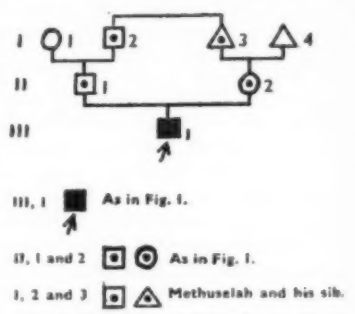

FIG. 2.—Lamech and his wife are shown as first cousins. Lamech must have inherited his recessive gene from his father, Methuselah, whilst BT'NWS inherited it from one of her parents, who is recorded as a sib of Methuselah.

The possibility that Noah inherited his albinism from a fallen angel need not be considered seriously. Such a supposition raises considerable genetic difficulties. One would have to postulate that BT'NWS and the angel were unrelated carriers of the gene at a time when it could not have been widely scattered, or, again, alternatively, and even less plausibly, that albinism in angels is

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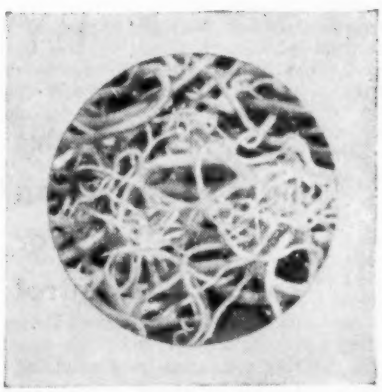

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dominant and not recessive as in man. Besides, it is not at all certain that albinism occurs in angels, other than seraphim. And clearly fallen angels are no seraphim.

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1 Genesis, v, 28-29.
2 The Book of Enoch the Prophet. Translated by R. Laurence, 3rd ed. Oxford, 1838.
3 Ibid., xii, 5.
4 Ibid., vii, 11.
5 Ibid., cv, 1-20.
6 Avigad, N., and Yadin, Y. *A Genesis Apocryphon*, 1956, p. 40. The Magnes Press of the Hebrew University, Jerusalem.
7 Ibid., p. 18.

HOSPITAL STERILIZATION

CONFERENCE AT SOUTHAMPTON

[FROM A SPECIAL CORRESPONDENT]

On December 17 the South-west Metropolitan Regional Hospital Board held a conference on "Hospital Sterilization" at Southampton University. It was attended by over 300 representatives of the medical, nursing, engineering, and administrative staffs of the hospitals in the region and by members of hospital management committees.

Opening the conference, Dr. J. REVANS, the Board's deputy S.A.M.O., said they had with them Brigadier J. D. WELCH, the leader of the Nuffield team whose report on sterilization practice in six hospitals* was about to be published, and he would give them a first-hand account of the results of this investigation. The audience would well appreciate the importance of the subject in view of the recent outbreaks of post-operative wound sepsis in the area due to both staphylococcus phage type 80 and *Clostridium tetani*.

Nuffield Investigation

Brigadier WELCH said that, when the Nuffield Provincial Hospitals Trust's operational research team started its investigation they decided to carry it out in three phases. The first was to look into present methods of sterilizing in hospitals. The second was to investigate the working of central sterile supply services on the Continent and in the U.S.A. The last phase would entail experimental trial of a central service in selected hospitals in this country. So far they had completed only the first phase, which was what he would discuss.

Six fairly typical hospitals had been chosen—a London teaching hospital, three large provincial general hospitals, and two cottage hospitals. The team had studied nurses at their sterilization tasks, making time studies and taking swabs for culture from all sterile equipment, instruments, dressings, etc. They had also studied conditions in ward sterilizing and sluice rooms, and had examined ward sterilizers, the storage of dressings, and the conditions of drums. A fairly intensive study had also been made of existing hospital autoclaves, their functioning and siting, and the people who operated them. The results of their investigations disclosed a disturbing situation, which Brigadier Welch illustrated by means of a film. It showed how haphazard were many of the methods of timing the boiling of instruments. The results of swabbing showed that 18% of all ward equipment, and 12% of all theatre equipment, was contaminated, figures which, he said, were fairly typical.

Autoclaving Technique Condemned

Autoclave departments were singled out for particularly heavy attack, not only by Brigadier Welch but also by all the subsequent medical speakers. They all stressed that immediate action was needed to correct this most unsatisfactory state of affairs. Much was due to the total lack of training of the autoclave operators, who were usually porters with other hospital jobs, most of whom had little idea of to whom they were responsible.

Brigadier Welch suggested the following short-term remedies that could be adopted immediately by hospitals at relatively low cost: (1) Improvement in the working of autoclaves. (2) Substitution of, say, steam-sterilized cardboard boxes for the present "iniquitous" hospital drums. (3) The introduction of central syringe sterilizing services. (4) Raising the standards of dressing techniques in the wards. (5) Better methods for the disposal of soiled linen and dressings. (6) The clear definition of responsibility in all sterilizing duties, particularly autoclaving.

Professor J. W. HOWIE (Glasgow), speaking on steam sterilization, discussed how a good autoclave should work. He preferred to discard the name "autoclave" and refer to the machines as high-pressure steam sterilizers. He called ward sterilizers "boilers," since they were not sterilizers: boiling did not totally destroy all forms of bacterial life, which was what sterilization meant. This could be accomplished only by exposing bacteria in dressings and instruments (both cutting and otherwise and including endoscopic instruments suitably protected) to dry steam or high-temperature steam under pressure. Provided this steam was at the high "phase boundary" temperature at which the change from water to steam occurred latent heat would be given out, and it was this which killed the bacteria. This vital fact was not generally appreciated. It was of the greatest importance that whoever was responsible for an autoclave should know the temperature reached in the chamber of the sterilizer. This information, which must be entered on the pressure-recording chart, was essential in order to assess whether the contents had been sterilized or not. Human errors were as much to blame for inefficient sterilization as mechanical, and modern over-reliance on antibiotics had led to a dangerous relaxation of standards.

The "Iniquitous" Drum

Professor C. A. WELLS (Liverpool), himself a surgeon, said that in the last few years surgeons had allowed themselves to become too complacent about post-operative sepsis. In any outbreak of sepsis responsibility should rest fair and square on the shoulders of the surgeons, who had been lulled into a sense of false security by the bacteriologists. Professor Wells then showed a film to illustrate faulty techniques in the wards, in autoclaving, and in the maintenance and storage of drums. He suggested the establishment of special "pre-operative wards," and supported Brigadier Welch's plea for the replacement of the "inquitous" drum by the cardboard boxes, which would stand steam sterilization under pressure at temperatures high enough to kill any spores of *Cl. tetani*. The cardboard boxes would be used as an interim measure until the introduction of special individual packs.

Another Horrifying Survey

In the afternoon Dr. E. M. DARMADY described the control and supervision of hospital sterilization carried out to-day in hospitals in the Portsmouth area. He illustrated his talk with some excellent slides of the many horrifying conditions found in present-day sterilizing practice, even in hospitals with good nursing standards.

A team consisting of a doctor, a bacteriologist, and a senior bacteriological technician under Dr. Darmady's supervision had carried out a survey similar in type to the Nuffield investigation. This team had focused its attention on ward sterilization techniques and the conditions under which nursing staff were expected to perform their sterilizing and dressing duties. These condition were both unfair to the nurses and dangerous: 20% of swabs from Cheatle's forceps were contaminated, 17% from syringes, 21% from instruments, 36% from bowls, gallipots, receivers, etc., and 24% from the contents of drums. Ward boilers were quite unable to sterilize efficiently, and this had been neatly demonstrated by attaching thermocouples to the instruments being boiled. Equally ineffective were the so-called antiseptic solutions used for cutting instruments. The proper cleaning of instruments by scrubbing them with soap and water before sterilization was important.

**Present Sterilizing Practice in Six Hospitals*, 1958, Nuffield Provincial Hospitals Trust. See also p. 1582 of this issue.

Ward Dressing Techniques

Ward dressing techniques in the different hospitals had also been studied, and in some they were antiquated and dangerous. Sometimes trolleys were laid out for as many as 15 consecutive dressings, a nurse merely covering them between dressings with a sterile towel from a dressing bowl on the trolley. Used dressings might be placed in uncovered bowls on the lower shelf of the trolley, remaining uncovered till the end of a long dressing round. A very high proportion of bed-pans had shown heavy contamination with faecal organisms after so-called cleaning either by hand or in standard bed-pan sterilizers.

Answering questions from surgeons on the sterilization of cutting instruments, Dr. Darmady said that exposure to steam at 190° C. for 1½ minutes would not blunt their edges. In a series of tests on "antiseptic" lotions used for storing such instruments all the solutions had grow *Cl. tetani* freely.

Mr. E. H. HURST, group secretary of the Portsmouth Hospitals, then gave the lay administrator's point of view. He said the "hidden costs" of the present methods of sterilization were enormous and not fully appreciated. They included the cost of maintaining and repairing ward boilers, apart from their high fuel consumption, and the large number of man-hours spent in operating and maintaining a series of autoclaves sited in different parts of a hospital. The only way for lay committees to deal with the problem was to take a lesson from industry and tackle it along the lines of work-study investigations. He agreed that the training and employment of autoclave attendants needed thorough revision. The present very low wage rates should also be reviewed so as to attract men of an altogether higher standard of intelligence.

A Matron's View

The last speaker was Miss DE LA COURT, matron of the Queen Alexandra Hospital, Portsmouth. She said that this was the first time in her 21 years as a matron she had attended a really tripartite discussion on the subject of sterilization. After hearing of some of the horrifying conditions still existing to-day, it seemed to her that we had gone back to the days before Florence Nightingale. One reason for the slackening in standards was the different teaching of nurses in different hospitals. One fact might be taught in the nursing schools and another on the wards. There was need for a uniform standard of teaching throughout the country. Regular "procedure" meetings, as at her own hospital, between matron, sisters, and staff nurses were helpful. Written reports of the meetings were circulated to all nursing staff and pinned up in sterilizing rooms.

Unfortunately there was no time for a general discussion. The conference was summed up by Mr. N. F. ADENEY (Bournemouth) and Dr. J. DOCKRAY (Isle of Wight).

Reports of Societies

HEBERDEN ORATION

PATHOGENESIS OF RHEUMATOID ARTHRITIS

This year's Heberden Oration was given by Professor CHARLES RAGAN, professor of medicine at Columbia University, New York, at the annual meeting of the Heberden Society on December 5. His theme was the role of hypersensitivity in the pathogenesis of rheumatoid arthritis.

Dr. Ragan recalled that four main theories had been advanced to explain rheumatoid arthritis. These were infection and focal sepsis; metabolic abnormality; endocrine abnormality; and hypersensitivity. His own working hypothesis of the pathology of rheumatoid arthritis was that it was primarily a vasculitis. In this context the theory of hypersensitivity was attractive, and the existence of the rheumatoid factor—which was a gamma globulin and which might be described as "an antibody to an antibody when the latter exists as an antigen-antibody complex"—made the theory more tenable. However, there were a number of difficulties.

There was no animal in which induced hypersensitivity could lead to *sustained* arthritis and vasculitis. The presence of vasculitis did not necessarily imply hypersensitivity, since Rickettsiae and even viruses could produce a widespread change of this type. All connective-tissue constituents so far tried had failed to produce anything resembling rheumatoid arthritis when injected into animals, even when adjuvants were used. Transfusion of the rheumatoid factor in volunteers did not produce disease, and patients with agammaglobulinaemia could get something that looked like rheumatoid arthritis.

If the rheumatoid factor were an antibody it was species non-specific. However, so were the thyroid antibodies described in recent years in connexion with thyroiditis. One of the biggest difficulties was that about 5% of the population of temperate countries showed a positive test for the rheumatoid factor without having rheumatoid arthritis, and many patients with the disease did not have the rheumatoid factor. In a recent incomplete survey of the native population of Liberia by Columbia University, no example of rheumatoid arthritis was found. Nevertheless 15% of the subjects showed a positive reaction for the rheumatoid factor as measured by the F II tanned sheep-cell agglutination reaction. In contrast the frequency of rheumatoid arthritis in the negro population in the United States was similar to that seen in the white population. Nevertheless, until the possible pathogenic role of the rheumatoid factor was thoroughly and completely disproved, it provided the only support for the implication of hypersensitivity in the pathogenesis of rheumatoid arthritis. If its role were disproved we faced a long, hard struggle which could be solved in the foreseeable future only with great luck and a dash of serendipity.

TUMOURS IN CHILDHOOD

Basing his remarks on the first five years' experience of the Manchester Children's Tumour Registry, Dr. J. K. STEWARD addressed the Manchester Medical Society (Section of Surgery), on November 11, on "Tumours in Childhood." Thanks to the reduction in frequency and seriousness of bacterial infections in children, tumours were now, he said, the second commonest cause of death between the ages of 1 to 15 years.

Since September, 1953, the Manchester Children's Tumour Registry had been collecting information about children in the North-west Hospital Region suffering from tumours. During this period they had registered 460 cases, representing 90% of the children certified as having died from tumours. Analysis showed that about one-third of the tumours were derived from the reticulo-endothelial system and another third from the nervous system. The overall mortality was at least 70%.

Sixty per cent. of the children were in hospital within two months of the start of their illness. On average a general practitioner saw a child with a tumour only once in 20 years, so earlier reference to hospital was unlikely to be possible. After admission any delay in diagnosis was very rare. He thought, therefore, that earlier diagnosis could probably contribute very little improvement to the results of treatment. Among the reasons why so many of the children were beyond hope of a cure when their condition was first diagnosed was that 84% of the fatal cases had either reticulo-endothelial or intracranial tumours, or tumours arising in the posterior abdominal wall. The poor prognosis of reticulo-endothelial tumours affected patients of all ages and was not just a problem of childhood. Of the intracranial tumours about half arose in, or involved, the brain stem or the third ventricle. Tumours of the posterior abdominal wall needed to attain a very large size

(Continued at foot of next page)

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Prednelan-N Injection (Glaxo).—1 ml. of this sterile suspension contains 25 mg. of prednisolone acetate and 5 mg. of neomycin sulphate. Because of its local anti-inflammatory action it is intended as an intra-articular injection in cases of rheumatoid arthritis, traumatic arthritis, osteoarthritis, and other similar conditions; the dose varies according to the size of the joint injected. The neomycin is added as a safeguard against infection, but the writer's preference is to maintain a strict sterile regime rather than to inject an antibiotic into a joint prophylactically.

N.H.S. basic price: six 1-ml. ampoules, 36s.

Mycifradin Tablets (Upjohn).
Neomin Tablets (Glaxo).
Nivemycin Tablets (Boots).

These are tablets of neomycin sulphate. When this antibiotic is given by the mouth little is absorbed, and it is in fact the most efficient of all intestinal antiseptics. It is superior to streptomycin, which can be administered by this route with similar results, in its "broad spectrum," its greater activity against certain bacteria (notably staphylococci and *Proteus*, but not streptococci), and in that bacterial resistance to it is rare, not readily acquired, and unaccompanied by resistance to any other common antibiotic. Its lack of sensitizing capacity and the fact that it is rarely given systemically are other advantages. It is chiefly used for suppressing the intestinal flora before operation on the colon. Two days' treatment is usually ample, and a daily total dose of 3 g. has been found satisfactory when measures are also taken to reduce the bulk and solidity of the bowel contents. Neomycin has also been given for much longer periods to patients with liver failure, in which benefit results from diminished formation of ammonia in the bowel. It can be used for the treatment of acute infections of the intestinal tract (*Shigella*, *Salmonella*, or, in infants, pathogenic *Escherichia coli*), though it is difficult to assess the relative merits of this and other antibiotics for these purposes.

N.H.S. basic price: mycifradin, 20 tabs. 0.5 g., 65s.; neomin, 20 tabs. 350 mg., 67s. 6d.; nivemycin, 20 tabs. 0.5 g., 65s.

Correction.—A note on "marcoumar" and "marevan" (December 13, p. 1471) described these anticoagulants as preparations of warfarin sodium. Marevan is, but marcoumar is not, though both are coumarin derivatives. We regret the error. Some of the details given in the note, and in particular dosage, are incorrect for marcoumar, whose dosage is much lower. It will be the subject of a note in this column at a future date.

(*Continued from preceding page*)

before they caused symptoms. The main reasons for the high mortality for tumours in childhood were therefore, it seemed, because they were reticulo-endothelial in origin or else arose in a situation where removal was impossible or where symptoms occurred late.

If surgery and irradiation were the only possible forms of treatment, the future for these patients would be very poor. However, the increasing success of chemotherapy in leukaemia was very encouraging. The fact that on rare occasions some tumours in children might regress spontaneously suggested that there was a natural resistance to their growth. Dr. Steward demonstrated a retino-blastoma which had regressed in this way.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Carbon-monoxide Poisoning

SIR,—Carbon-monoxide poisoning is very important because it is so common. Nine people die of it, on average, every day in England and Wales and there are many more non-fatal cases. In 1957 carbon-monoxide deaths totalled 3,409[1]—nearly three times as many as caused by all other kinds of poisoning combined. For every three deaths from road traffic accidents, which cause such public concern, there were two deaths from carbon monoxide.

The proper treatment of this condition is obviously a matter of great importance. For many years it has been accepted as being the inhalation of 7% carbon dioxide in oxygen (carbogen) which very greatly increases pulmonary ventilation and speeds clearance of carbon monoxide from the blood. It has long been recognized that the main life-saving application of this treatment is by first-aid workers, because severely poisoned patients will die, or be beyond recovery, by the time they get to hospital if carbogen treatment is not started by those who first reach them. Unfortunately, in this country carbogen was removed from ambulances and first-aid services several years ago on direction, privately circulated to authorities, of the Breathing Apparatus Committee of the Medical Research Council. The medical profession as a whole was not informed by publication in the medical press till four years later.[2] The official advice was then challenged.[3] Now, after nearly four more years, the Council has just issued a statement (*Journal*, December 6, p. 1408) reversing its former advice and advocating restoration of carbogen.

The Council's statement does not set forth the evidence which has caused this change of mind. This is a serious omission, because restoration of 7% carbogen is not advised and it is said: "In the light of present knowledge the subcommittee do not consider that there is anything to be gained by the use of higher percentages [than 5%] of carbon dioxide in oxygen." It might seem that the difference between using 5% and 7% carbogen is unimportant. *In fact, it is a matter of very great consequence, because saving of life may be reduced to about one-third of what it might be.*

When carbogen first displaced oxygen, nearly 40 years ago, as the accepted treatment of carbon-monoxide poisoning, it was used in 5% strength. Later, it was found that 7% produced very much more vigorous breathing and should therefore be considerably more effective, because the speed of elimination of carbon monoxide is related to the pulmonary ventilation. It was shown that the curve of increased breathing in response to inhalation of carbogen mixtures of increasing strength in unpoisoned individuals rose gently up to 5% (the amount of carbon dioxide normally present in the lungs) and then very steeply from 5 to 7%. In these normal subjects 7% carbogen doubled or trebled the pulmonary ventilation produced by 5% carbogen and caused the volume of respiration to increase to about seven times the amount when air or oxygen alone was breathed.[4,5] These findings needed confirmation in patients poisoned by carbon monoxide in case the poisoning should produce some radical alteration in response. The emergency conditions of very severe poisoning in human beings precluded strictly comparable experimental studies, but survival was regarded as being perhaps the ultimate criterion. A large-scale practical trial was carried out in New York[6] by specially trained resuscitation crews over a period of eight years, during which 7,845 poisoned patients were treated. In the three years 1926 to 1928, 5% carbogen was used in treating 2,854 patients, and there were 234 deaths (82 per 1,000). In the next five years 7% carbogen was used for 4,991 patients, and 156 deaths occurred (31 per 1,000)—i.e., the deaths were reduced to almost one-third of what they would have been had 5% continued to be used. For the last quarter of a century 7% carbogen has been used in treating a very large number of patients all over the world.

The Council surely should not advise 5% carbogen unless it can quote evidence adequate to refute the New York experience. It is therefore pertinent to ask for the results of whatever experiments were done to compare the efficacy of 5 and 7% carbogen. If the Council still persists in giving advice contrary to accepted opinion, then, I submit with respect, the responsibility lies upon it to produce irrefutable evidence to support its attitude. It would not so much matter if its statement was just an expression of opinion, but it will be taken as *official direction* on which executive authorities will act all over Britain.

It would seem possible that the Council has not yet fully rid itself of the fear that carbogen may cause carbon-dioxide poisoning in cases of carbon-monoxide poisoning "in respiratory failure." This alleged danger was stressed in the Breathing Apparatus Committee's report,[2] but it was merely presumed from theoretical considerations and no direct factual evidence was presented. Now that some practical research has been done, the Council's statement admits that respiratory failure either never occurs in carbon-monoxide poisoning or is so rare and so brief as to have only academic significance. Most forms of asphyxia, other than carbon-monoxide poisoning, are accompanied not only by oxygen lack but also by obstruction to carbon-dioxide excretion, and in them, as the Committee rightly stated, oxygen alone should be used. This is not in dispute. But carbon-monoxide poisoning is a special, though very important, type of hypoxia in which there is massive bar to oxygen uptake but little or no interference with carbon-dioxide output.

7% carbogen causes very great increase in breathing within a few seconds of inhalation. Its speed of action is most urgently needed in severe cases because they are very near to dying from damage to vital organs by extreme oxygen deprivation. Fortunately, carbogen administration is simple for first-aid workers to carry out anywhere, given suitable portable apparatus, and easy to maintain in the confined space of an ambulance or mine. The increased pulmonary ventilation which 7% carbogen produces is very much greater than can be achieved by manual artificial respiration, though this may sometimes be needed to start carbogen inhalation in dying patients or in attempting to revive those who seem dead. First-aid workers need instruction in the use of carbogen and require particularly to be taught that its administration must be started instantly. They also need to be impressed that patients poisoned with carbon monoxide look *deceptively well*; they have a good colour and quiet breathing and may seem no more than confused, stuporose, or sleeping. Nevertheless, they need immediate carbogen treatment.

I am sorry, Sir, once more to write about this matter, and only do so because I firmly believe that many needless deaths will continue to occur if 7% carbogen is not restored. Medical officers who have the duty of determining the equipment of ambulances and other first-aid services might well weigh carefully their responsibility before they issue orders to re-equip with 5% carbogen instead of 7%. They and the rest of the medical profession should have the opportunity of examining evidence when official direction is contrary to generally accepted opinion.—I am, etc.,

London, W.1. H. L. MARRIOTT.

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SIR,—The statement by the Medical Research Council and your annotation (*Journal*, December 6, pp. 1400 and 1408) on the use of carbon-dioxide–oxygen mixture in carbon-monoxide poisoning are interesting and of value in the first-aid treatment of gassing cases, but are lacking in practical guidance to those concerned in providing first-aid services.

It is all very well for the Medical Research Council to repeat that "it should not in practice be difficult for first-aid workers to distinguish between these two groups of patients," when deciding whether the mixture or pure oxygen is the correct treatment, but what is implied is that the first-aid workers will have both carbon-dioxide–oxygen mixture and pure oxygen with them at the time. This means duplicating the resuscitation sets and cylinders.

The practice of carrying cylinders of the mixture in ambulances was discontinued and oxygen was substituted on the last recommendation of the M.R.C. on this subject, and in industry the same procedure was carried out. Have the ambulance services and industry now to carry both? This would mean a great increase in expenditure initially, and in maintenance, and is this really justified when the M.R.C. report states that "the differences in practice between the effectiveness of the two methods of treatment are almost certainly small"? Could we not have a more practical authoritative statement on this subject—as to whether first-aid services should have the added expense and upkeep of maintaining two types of resuscitation equipment, or whether, taking all factors into account, oxygen alone is not sufficient?—I am, etc.,

Sheffield, 10. JAMES GREGORY.

Afibrinogenaemia after Transfusion

SIR,—Mr. James M. Moore's paper in your issue of November 15 (p. 1201) is doubtless of much value to those concerned with blood disorders. I would like to know why a young woman of 25, apparently in good condition, needed two pints (1.1 l.) of blood during and after a planned gastrectomy? Mr. Moore says her condition was good after the operation and that there was little blood lost—as one would expect. Why, then, transfuse her? Will Mr. Moore please tell us?—I am, etc.,

Worcester Park, Surrey. H. J. FRIEND.

SIR,—I was particularly interested in the account of a fatal case of uncontrollable post-operative haemorrhage after incompatible transfusion by Mr. James M. Moore, which appeared in the *Journal* of November 15 (p. 1201). Some years ago I was concerned in an investigation into three similar deaths. All three followed major thoracic surgery. All three had been transfused with many pints of stored citrated blood over a short period of time—i.e., 3–4 hours. All three had a clotting defect, and in all three the type of haemorrhage was identical with that described—namely, a general oozing over the whole area of trauma. None of the three cases received any incompatible blood and none received any dextran. At the time of this investigation I made the tentative suggestion that future cases of uncontrolled concealed haemorrhage might be transfused with fresh heparinized blood, the advantage of heparin over citrate being that it can be neutralized *in vivo* if necessary.

I have reason to believe that this regime was adopted with considerable success by one of the leading teaching hospitals. I myself have only had the opportunity of observing the effects of such treatment on one case. This was a young man aged 28 who was admitted to hospital after a severe melaena. He was transfused with many pints of stored citrated blood over a period of about a week, but continued to bleed. After two pints (1.1 l.) of fresh heparinized blood the haemorrhage ceased and he was eventually brought successfully to operation. At operation he was found to have a large carcinomatous growth in the stomach which eventually killed him.

In Mr. Moore's case the operation was completed at 12 noon. During operation one pint (0.6 l.) of blood was transfused. "The patient's condition was good immediately after operation which had *not* been associated with significant loss of blood." A second bottle of blood was started at 12.30 p.m. I think it is generally agreed that if a patient requires only one pint of blood then blood is not essential. One must therefore ask the question, Why any blood at all in this case and why a second bottle? Has not the time arrived when the medical profession generally should give serious consideration to the extravagant use of blood with all its concomitant risks in general surgery? Am I old-fashioned in suggesting that blood should only be transfused when it is essential to save life?

Although it was right and proper, it is particularly unfortunate in this case that it was necessary to draw attention to the somewhat doubtful evidence that dextran can produce a haemostatic defect, for it would appear that this was the ideal type of case where a little dextran would have been adequate to maintain this patient's condition. The dextran administered to this patient could have played no part in the result, since the coagulation defect was known to be present before it had been transfused. Furthermore, although some interaction between dextran and fibrinogen has been demonstrated *in vitro* at very low temperatures, this has never been shown to occur at body temperature or *in vivo*. If my memory does not play me false I believe it is correct to state that the only haemostatic defect which has been found in patients transfused with dextran has been a prolongation of the bleeding time, the cause of which was obscure. A number of such cases concerned volunteers with a normal blood volume who were transfused with 0.5 to 1 litre of dextran. It will be understood, therefore, that following transfusion the cardiovascular system of these volunteers was considerably overloaded. Such cases therefore bear no true relationship to cases transfused with dextran in order to combat hypovolaemic shock.

Dextran has now been used with success for the treatment of many thousands of cases of hypovolaemic shock either alone or in combination with blood. For this purpose it has proved itself to be a cheap, reliable, and very valuable therapeutic agent which is free from the many dangers associated with blood and plasma. It is suggested therefore that dextran could replace a great deal of the blood used to-day with benefit to all concerned.—I am, etc.,

London, N.W.3. S. G. RAINSFORD,
Late Director of the Royal Naval Blood Transfusion Service.

B.M.A. Clinical Meeting

SIR,—The perhaps faintly apologetic tone of the first paragraph of your leading article in the *Journal* of December 13 (p. 1457), commenting on the inaugural Annual Clinical Meeting of the Association, I confess disturbs me. From it I am to gather that, "not insensitive" to the critic who says that "an organization costing a quarter of a million pounds a year" is "spending too much of its energy on getting more money for doctors," those responsible for the conduct of B.M.A. affairs have, as a kind of partial answer, instituted this purely scientific and clinical meeting.

It is doubtless purely lack of space which prohibited you, having once raised this question, from administering the full and final real answer to any such critic, which is historical.

Forty years ago the B.M.A. was urging better facilities for treatment, particularly for the poor. The Government's Dawson Report[1] (1920) resulted, abortive as regards any implementation. In 1930 the Association produced its Proposals for a General Medical Service for the Nation,[2] revised for a second edition in 1938: and then came the Beveridge Report[3] (1942) and the Act of 1946.[4]

Now, Sir, as one privileged to be present at every debate by the Representative Body on all these Government or B.M.A. schemes from the first-mentioned to the last, I wish to emphasize that it was an outstanding and striking feature that all these annual debates confined themselves entirely to matters of fundamental principles in the endeavours to formulate schemes in the public interest which at the same time could, on broad principle, be acceptable to the profession: indeed, none of the above documents discuss remuneration except perhaps to say that arrangements would have to be made.

This feature of the Representative Body debates ever commanded my own admiration, though it was much criticized at our periphery. It was only when, faced with revolutionary governmental proposals, the profession at last reached the stage demanding public negotiation of remuneration for all that was to be required of it that Spens, in two main reports,[5,6] hit the headlines in a matter of deep national concern. Hence, Sir, the unwonted prominence of the money questions to-day; and hence also the critics whom you cite, nearly all of them ignorant of the Association's true record of quiet background energy expended in these matters for forty years, a record which, in fairness, cannot be too widely stressed.—I am, etc.,

Newquay, Cornwall. F. A. ROPER.

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Inorganic Arsenic

SIR,—On several recent occasions I have seen and heard about arsenical keratoses, pigmentation, and multiple epitheliomata in adult patients. On inquiry, I am informed that in two recently observed cases the patients (both women) had received medicine containing arsenic over a period of time many years ago and that it is now known that arsenic, very gradually and perhaps after an interval of many years, may cause the epithelial disease noted. In fact, the content of the arsenic is greater in those sites in which superficial epitheliomata occur than in other parts of the skin.[1] In conversation I was informed that arsenic is still sometimes recommended as a dermatological remedy.

Is there, in fact, any evidence of even the slightest value in inorganic arsenic medication? I was somewhat alarmed to see in *The Extra Pharmacopoeia, 1958*, that there are still four preparations containing inorganic arsenic, and even in the *British National Formulary, 1957*, it says (p. 116):

"When Mist. Ferr. Arsen. is prescribed, Mist. Ferr. et Ammon. Cit. containing Arsenical Solution, 3 m. in each 1/2 fl. oz., shall be dispensed."

In view of the possibilities of remote dermatological disease of a serious nature arising from arsenic, given perhaps many years before, would it be wise to reconsider most carefully whether inorganic arsenic should be abolished from the *Pharmacopoeia*?—I am, etc.,

Department of Child Health, University of Bristol. A. V. NEALE.

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Cancer Survival Rates

SIR,—I would like to draw attention to the situation that has arisen from the practice among some writers of attempting to correct the "crude survival rates" in ordinary use, by making use of the probability that some of those who died before the expiration of say "x" years died from some other cause than cancer. Dr. Percy Stocks[1] suggested that the factor p_0 based on vital statistics and introduced by Berkson in 1942 could be applied to the data in question. The application of this factor can result in the anomalous conclusion that a 10-year survival rate can exceed its associated 5-year rate.[1,2] This seems devoid of common sense.

This is a matter of serious concern. Some of the hospital boards prepare annual reports about the results of cancer treatment, others are preparing to follow suit. The need for a method of presenting results in a manner free of anomaly is a real one. It is significant that the W.H.O. figures published periodically are expressed in "crude survival rates." Those coming from Radium Hemmet, Stockholm, are in the same form. It may be that there is a more essentially true form of rendering the data than this, but until it has been tested and agreed upon is it not desirable to continue with the crude rates?—I am, etc.,

Bognor Regis. SIDNEY RUSS.

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Antibiotics in Acute Tonsillitis and Otitis Media

SIR,—In the recent correspondence about the treatment of otitis media initiated by Dr. John Fry's most valuable article (*Journal*, October 11, p. 883) I have seen no mention of myringotomy, and wonder whether this has now been completely discarded. Recurrence of otitis media in cases which I had thought adequately treated with antibiotics led me this year to do a myringotomy as well in all but the mildest cases, and, although one can hardly judge the value of it yet, I find a definite note of "pus present" in 10 cases out of 27 and "thin fluid" in another two. Previously I should have treated all these patients with antibiotics alone, and can well picture the formation of a jelly-like mass as described by Dr. Peter A. Walford (*Journal*, November 29, p. 1353). After reading his letter I am all the more doubtful of using antibiotics in this condition unless a perforation is present, whether natural or artificial.—I am, etc.,

Hereford. A. F. STALLARD.

Decline of Pertussis

SIR,—Professor A. D. Gardner's letter in your issue of September 13 (p. 688) headed "The Decline of Pertussis" has interested me. After being in general practice in England for many years, I have worked in Tanganyika for the last 1½ years as a Mission doctor in an up-country station. I have compared the incidence of whooping-cough in these two places. Here whooping-cough appears to be the most frequent of the infectious diseases of childhood, with a seasonal prevalence from September to December. It occurs most frequently between ages 2 to 6. In addition to its prevalence, its severity is very noticeable and is in great contrast to my experience of it in England. The attacks of whooping are very distressing to witness, the spasms so prolonged before ending in vomiting. The children have generally been ill many days before being brought to hospital. Fatality has occurred only amongst the younger children, but the incidence of resulting morbidity must be high in patients of all ages.

Up to the present no preventive inoculation has been used here. However, I have recently started inoculating a few children and hope to extend this work. Expense is restricting, but the belief which I share with your correspondent that inoculation is so worth while is encouraging.—I am, etc.,

Handeni, Tanganyika. JESSIE E. PRINGLE.

Medicine on Television

SIR,—Everybody will agree with your correspondent Professor Roger Warwick (*Journal*, November 29, p. 1354), that medicine should not be turned into a "peepshow," but, judging from Mr. Dickson Wright's remarks at the meeting, it would seem that he lives in the world of fifty years ago. Surely the first thing to decide is what is the objective to be aimed at by bringing medicine before the public, by means of television, radio, lectures, newspaper articles, etc.? I suggest that the prime object should be to get rid of or at least diminish fear of disease.

To do this, all drama must be taken out of medical displays and talks. The slightest suggestion of the dramatic builds up the idea of "crisis," which leads to fear. In the old days the public had greater faith in their doctor, and to be told that there "was nothing to worry about" was sufficient. The days of the "High Priest" are gone, and to-day it is necessary to use a different technique—namely, to appeal to the common sense of the patient. Too many family doctors treat their patients as idiots. I realized this after lectures to the public (84 this year so far), when in conversation with members of the audience. For example, on more than one occasion it has been said, "I could not possibly talk to my doctor about cancer. I hate being laughed at." Many people have spoken in praise of the television series *Your Life in Their Hands*. There is much still to be learnt about the best way of "putting it across" by these various publicity methods, and Dr. C. M. Fletcher is undoubtedly right in advocating more scientific surveys of the results.—I am, etc.,

Oxford. MALCOLM DONALDSON, Hon. Secretary, Cancer Information Association.

Chlorothiazide in Epilepsy

SIR,—The clinical effects of "diamox" (acetazolamide) and "saluric" (chlorothiazide) on sodium and water metabolism seem to have some similarities. In addition the former has been found useful in the treatment of idiopathic epilepsy. In the hope that chlorothiazide might also be beneficial in control of idiopathic epilepsy, we tried this drug in six female patients suffering from this disorder.

Out of a ward of 50 epileptics, six patients who satisfied the criteria of suffering from chronic idiopathic epilepsy without any other disorder were selected. The average age of patients was 48 years and the average duration of hospitalization was 12 years. In three of them the main problem was frequency of fits (average of three fits a week) and in the other three it was the marked disturbance of behaviour (e.g., impulsiveness, constant quarrelling, physical violence, destruction of property, etc.). All had been tried on the well-known anticonvulsant drugs without much beneficial effect. During the trial these drugs and the patient's environment were unchanged. Each patient was given 500 mg. of chlorothiazide orally each morning, four mornings a week. Record of patients' behaviour and fits was charted on a specially designed item sheet consisting of 30 items, by the same observer throughout. After a trial of eight weeks no patient showed any appreciable change either in frequency of fits or behaviour disturbance; there were also no untoward side-effects noted clinically.

It is well known that acetazolamide has a marked generalized antagonistic effect on carbonic anhydrase, an action very feebly shown by chlorothiazide. In this may lie the explanation of the failure of chlorothiazide in epilepsy. It also appears that the salt–water depletion and diuresis brought about by both these drugs contribute little, if at all, towards amelioration of epilepsy.

The work was carried out at Cane Hill Hospital, Coulsdon, Surrey, and the drug was kindly supplied by Messrs. Merck Sharp and Dohme Ltd., Hoddesdon, Herts.

—We are, etc.,

Warlingham Park Hospital, Warlingham, Surrey. N. H. RATHOD. ANDREW SKARBEK.

Toxic Psychosis after Atropine Eye-drops

SIR,—Drs. J. P. Baker and J. D. Farley (*Journal*, December 6, p. 1390) have drawn attention to the psychiatric aspects of atropine intoxication, following prolonged topical exhibition of the drug in ophthalmic practice. Their suggestion, "that closer investigation might be made into the origin of states of minor emotional disturbance, usually attributed to psychological stress, in patients undergoing eye surgery with prolonged routine atropinization," merits comment.

In my personal experience the majority of cases of mental disturbance amongst ophthalmic in-patients occur after cataract extraction in the elderly, episodes of senile dementia coming on within two to four days of operation. Atropine may not have been exhibited at all, or, at the most, only as daily instillations since operation. Retinal detachment cases rarely show psychotic symptoms, as occurred in the case Drs. Baker and Farley describe; their reactions appear to be the responses of differing personalities to the extreme tedium of the post-operative regime, and they revert to normal promptly as soon as the patient is allowed more freedom, although topical atropine is continued.

Clearly atropine must be regarded in future in the same light as hyoscine, which is occasionally responsible for the sudden appearance of psychotic symptoms. The problem is one of idiosyncrasy involving a few patients only, and leaves untouched the larger issue of the management of senile ophthalmic in-patients.—I am, etc.,

Moorfields Eye Hospital, London. D. W. HILL.

Artificial Insemination

SIR,—Members of the Association will recall that the Annual Representative Meeting passed the following resolution:

310. **Resolved:** That this Meeting, while making no pronouncement on the non-medical aspects of A.I.D., authorizes the Council to submit evidence to the Government Committee on this subject from the medical point of view, if so requested.

A request has now been received by the Association from the Departmental Committee set up by H.M. Government to submit evidence, and the Council has decided to do so, within the terms of the foregoing resolution. The Science Committee has been asked to inform the Council on the medical aspects of A.I.D., and to enable it to do so it is anxious to collect as much up-to-date evidence as possible. As chairman of that committee, I am writing to seek the assistance of any practitioner who is in a position to provide it on a particular aspect of the problem. The committee is most anxious to obtain evidence on the subsequent psychological well-being, or otherwise, of any married couple who have availed themselves of A.I.D.—and, even more important, the subsequent effects on the child or children born as a result. May I ask any family doctor who has such a family under his care to supply the committee with written evidence bearing on this point. The committee will be most grateful for all such help, which will, of course, be treated as confidential in the highest degree.—I am, etc.,

J. R. NICHOLSON-LAILEY,
Chairman of the Science Committee of the B.M.A.

B.M.A. House,
Tavistock Square,
London, W.C.1.

Tuberculous Meningitis after B.C.G.

SIR,—I wish to endorse the opinion of Dr. H. G. Calwell (*Journal*, November 29, p. 1356) regarding the paper on "Tuberculous Meningitis Following B.C.G. Vaccination" by Drs. Mary R. Kerr and J. M. Dunbar (*Journal*, October 25, p. 1019). In Dublin city 85,038 children and young adults were B.C.G.-vaccinated from October, 1948, to October, 1958, and in the whole decade no case of tuberculous meningitis and no death from any form of tuberculosis occurred in this large number of vaccinated personnel.

We have always adhered to Calmette's teaching, as expressed by Professor Robert Debré in his letter in the *Journal* of November 22 (p. 1292), and strict isolation periods have been observed in all cases that had exposure to home infection. In my opinion, the tuberculous meningitis case described by Drs. Kerr and Dunbar serves as a warning to all B.C.G.-vaccinators not to omit pre- and post-vaccinal isolation in these home-contact cases. When these isolation periods are observed, as in Dublin and Belfast, there is no incidence of tuberculous meningitis in B.C.G.-vaccinated personnel.—I am, etc.,

M. DUNLEVY.

Tuberculosis Section,
Corporation of Dublin.

Hospital Blankets

SIR,—Could not some contamination be avoided if blankets were put into zipped cotton cases? Blankets could be kept smooth by use of blanket pins or clips. Perhaps a bottom blanket could be replaced by the easily boiled cotton quilted pads used for this purpose in hospitals in the U.S.A. —I am, etc.,

K. F. BURN.

Oxford.

Coloured Signals

SIR,—Between October and December, 1957, there was a correspondence in *The Field* of considerable medical interest. Some contributors described the flash of green light seen just as the sun was rising or setting over the sea, and one suggested that this was due to the last yellowish rays blending with the blue of the water. But, arising out of this, another contributor described how, when driving behind another car at night, he had a momentary impression of green as its tail lights disappeared. And another, with memories of night operations in the first war, remarked that eye fatigue in the small hours was far from rare.

Might the eye tire for some colours faster than for others? Inquiry from an expert established that this phenomenon of apparent colour change is quite well known; he also stated that if a red light is observed through a moving screen it may appear green, the converse also occurring. Can we be certain, then, that a train driver seeing a light known to be red through the lattice work of a bridge, which lattice work was crossing his field of vision, might not report the wrong colour—red for green and green for red? And might not a fireman, after looking too long into the fire, have a momentary fatigue of the eye for red?—I am, etc.,

G. C. PETHER.

Hitchin, Herts.

Chloroquine in Rheumatoid Arthritis

SIR,—The article by Drs. H. Fuld and L. Horwich entitled "Treatment of Rheumatoid Arthritis with Chloroquine" (*Journal*, November 15, p. 1199) is a type of study that appears commonly in journals both in this country and in Great Britain. It is a type of study that is responsible for the multiplicity of drugs used in rheumatoid arthritis and for the many types of therapy which give in the hands of most practitioners only indifferent results.

Those of us who work extensively with rheumatoid arthritis know that it is subject to many influences: the emotional state of the patient, the season of the year, the barometric pressure, the weather, the financial status of the patient, the presence or absence of secondary infections, the presence or absence of epidemic upper respiratory infections in the community, and other factors which do not occur to me now or of which I am ignorant. Certainly one of the most important factors is the enthusiasm and friendliness of the attending physician. If he is dull and disinterested, but with little hope for improvement for the patient, his patients do not do well. On the other hand, should he be experimenting with a new medication, and should he have a spirit of enthusiasm and hopefulness, should he inquire with interest in all the symptoms of the patient, should he listen with care to their complaints, and should he examine their painful joints with more than usual devotion, the patient almost always responds by some degree of subjective improvement. We have seen this time and time again in a large metropolitan arthritis clinic.

Therefore, no study on the effectiveness of a drug or method of treatment of rheumatoid arthritis is of value unless it is combined with a controlled study of untreated patients. The doctor himself must not know which are the ones receiving treatment and which are the ones that do not. The number of cases in both the controlled and the treated groups must be statistically significant. Otherwise there will be no end to the types of treatment which enthusiastic physicians will recommend on the basis of various uncontrolled and superficially convincing reports.

I find the recommendation of chloroquine not especially disturbing, since, in our own experience with it, we found no serious toxic results, although it was of little benefit. The recommendation, however, of blood transfusions is very disturbing, since all transfusions carry a danger of homologous serum jaundice. I am unaware of any valid study which establishes the value of such a definitely hazardous method of treatment of rheumatoid arthritis.—I am, etc.,

R. R. MERLISS.

Cedar of Lebanon Hospital,
Los Angeles.

Christabel Pankhurst Memorial

SIR,—Last month will be remembered in our constitutional history as the one in which women first sat as members of the House of Lords. This event calls to mind the advance that women have made in status in recent times. In the nineteenth century they were regarded in effect as second-class citizens. But step by step during the last 50 years legal discriminations have been removed until to-day very few remain.

We recognize the debt we owe to the pioneers who pressed women's enfranchisement on reluctant Governments. Notable among them was Christabel Pankhurst, who as a young law student struck a new note of defiance by adopting

what later came to be known as militant tactics and thereby made "Votes for Women" front page news. During the nine years in which the conflict raged she displayed courage, political insight, and leadership to a high degree, and devoted the whole of her youth to obtaining the enfranchisement of her sex.

The older generation of doctors will recall that one of the Pankhursts' earliest supporters was Dr. Elizabeth Garrett Anderson, who suffered imprisonment in the cause. They will also recall the influential committee of doctors, headed by Sir Victor Horsley and Dr. Haden Guest, to bring pressure on the Government to stop the brutality of forcible feeding as done by prison authorities. Doctors, both men and women, were splendid in the assistance they gave to the suffragettes released from prison in shocking condition, and in dealing with injuries sustained when thrown out from political meetings.

Dame Christabel died a few months ago, and many people feel that a national memorial should be erected to her. We have therefore formed a committee, of which Lady Pethick-Lawrence is treasurer, to raise a fund for this purpose. This committee is representative of women prominent in all professions in life. Lady Astor, Miss Rose Heilbron, Dame Vera Laughton Mathews, D.B.E., Dame Sybil Thorndike, D.B.E., together with women M.P.s and old suffragettes, and with Dame Christabel's young cousin, Miss Goulden Bach, as secretary.

I am glad to be chosen to represent the women doctors, and I hope both men and women members of the profession will be staunch to-day in support of this memorial, and send their cheques to our Treasurer, at 11, Old Square, Lincoln's Inn, London, W.C.2. Our proposal, which has been approved in principle by the Ministry of Works, is the addition of a semicircular low wall to Mrs. Pankhurst's statue in Victoria Tower Gardens adjacent to the House of Lords. The wall will terminate in two piers showing on one a bronze relief of Dame Christabel, and on the other a replica of the Women's Social and Political Union prison brooch. The design appears to be particularly appropriate, for, inasmuch as Christabel and her mother jointly led the militant campaign, so should they be remembered together by future generations.—I am, etc.,

London, W.1. A. LOUISE MCILROY.

Onset Enuresis

SIR,—The statistics produced by Drs. J. D. Paulett and E. Tuckman (*Journal*, November 22, p. 1266) are impressive; but before we are tempted to conclude that onset enuresis results from raising the poor above their station it would be interesting to hear that it is less frequent in a poor population which has not been recently re-housed. The writings of some workers—for example, Spinley[1] and Kerr[2]—indicate that it is far from unknown.

We find it impossible to recollect, to a greater accuracy than plus or minus one year, the age at which our two sons, now aged respectively 8 and 14, became reliably dry at night. Has a scientific training made us less observant than the patients who contributed to Dr. Tuckman's third table, or more preoccupied, or just less willing to commit ourselves to a categorical statement?—We are, etc.,

KENNETH ULYATT.
London, S.E.27. FRANCES MARGARET ULYATT.

REFERENCES

[1] Spinley, B. M., *The Deprived and the Privileged*, 1953. London.
[2] Kerr, M., *The People of Ship Street*, 1958, London and New York.

POINTS FROM LETTERS

Hypnotherapy

Drs. GORDON AMBROSE and GEORGE NEWBOLD (London, W.1) write: Dr. William Sargant's review of our book *Hypnosis in Health and Sickness* (*Journal*, December 6, p. 1396) was very like the curate's egg. We would like to correct one or two points in the review. It is not made absolutely clear that (and here we quote from the preface) " . . we felt the time was ripe for the publication of a work which would present *to the public*, so far as our limitations permitted, a reasonable picture of the place of hypnotherapy in modern medicine." Dr. Sargant recites a long list of subheadings from two chapters, and possibly implies that hypnosis is seen by us as a panacea for all ills. We have been particularly careful in all our writings to refute this claim.

Obituary

G. H. G. SOUTHWELL-SANDER, M.B., D.P.H. D.I.H.

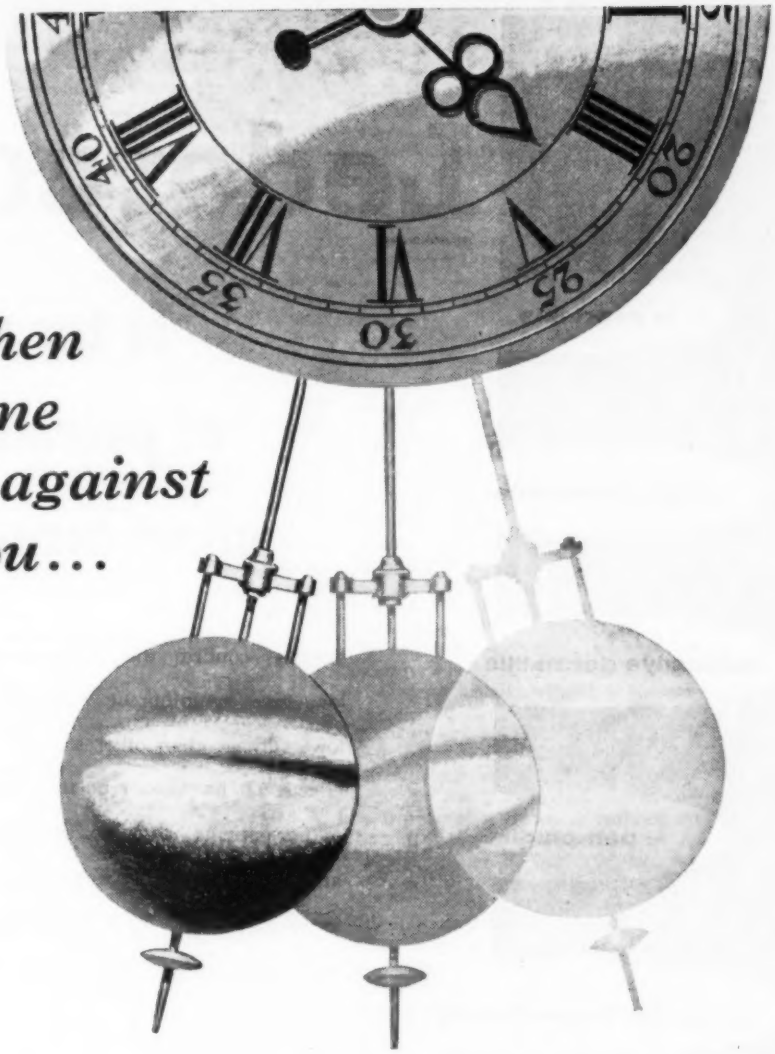
Surgeon-captain G. H. G. Southwell-Sander, who did much to improve working conditions in the dockyards and ships of the Royal Navy, died suddenly at his home near Dorking on December 6. He was 53.

Geoffrey Henry George Southwell-Sander was the only son of the late Dr. G. A. Southwell-Sander, who practised in Wateringbury, Kent. From Charterhouse he went on to Caius College, Cambridge, and then to St. Thomas's Hospital, qualifying in 1930 and graduating M.B., B.Ch. in 1931. He was house-physician at the Brompton Hospital, house-surgeon at the Royal Victoria and West Hants Hospital, Boscombe, and a resident medical officer at the sanatorium at Milford in Surrey. His interest in tuberculosis led him to a wider view of preventive medicine, and he took the D.P.H. at the London School of Hygiene and Tropical Medicine in 1933. After a short spell in his father's practice near Maidstone he entered the medical service of the Royal Navy late in 1933. Not long afterwards, to his great satisfaction, he was sent out to the China Station and spent some time up the Yangste. On his return home he married Elsie (Jackie) Graham, daughter of Dr. James Graham, and worked for a time in London as a house-physician at the Postgraduate Hospital at Hammersmith. His one and only hospital appointment in the Navy was that of clinical pathologist at the R.N. Hospital, Bermuda, where he served from 1938 to 1941, carrying out his duties there with characteristic thoroughness, zeal, and ability. Later in the war he saw active service in the Arctic and elsewhere. His subsequent career was mainly in the fields of preventive medicine and industrial health.

R. L. G. P. writes: The sudden death of Geoffrey Southwell-Sander has come as a great shock and brought much distress to his many friends, both inside and outside the Service. His health had been far from robust for some years, but he did not allow this sombre handicap to interfere in any way with the high standard of work which he incessantly maintained throughout his life.

It was while serving in the Medical Department, Admiralty, from 1943 to 1944 that his interest in industrial medicine became enthusiastically stimulated. He obtained the D.I.H. in 1950, and there is no doubt that he put industrial medicine on the map so far as the Royal Navy is concerned. He emphasized the opportunities in this direction that arise in H.M. dockyards, H.M. aircraft repair yards, and last, but not least, in H.M. ships themselves. He fully appreciated the fact that preventive medicine is second to none in the practice of medicine, and he was constantly endeavouring to the best of his ability, which was considerable, to put this conception across to all and sundry. He was one of the original members of the Joint Services and Factory Committee on Occupational Health, which consists of Service members from the three fighting Services and civil experts in various fields of industrial medicine. He did good work in H.M. Dockyard, Singapore, and the Naval Base from 1950 to 1952, but it was while holding the appointment of senior medical officer, H.M. Dockyard, Portsmouth, from 1952 to 1955 that he achieved outstanding success. He reorganized the medical section of the dockyard, and was of the greatest help to the Medical Director-General during the period when the Home Dockyard Regulations were being revised and brought up to date. Old routine measures were dropped, and modern views were introduced, largely as the result of Geoffrey Southwell-Sander's personal experience in industrial medicine.

In 1955 he rejoined the Medical Department, Admiralty, as assistant to the Medical Director-General in hygiene, preventive medicine, and industrial medicine. A year



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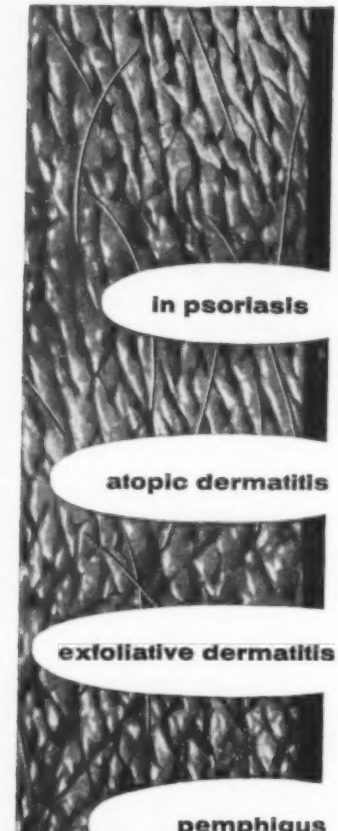

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[1] *J.A.M.A.* 165: 14: 1821-1823 (Dec. 7) 1957.
[2] *J.A.M.A.* 167: 8: 959-964 (June 21) 1958.

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later he was elected president of the Services Group of the Society of Medical Officers of Health: his presidential address on "Preventive Medicine in the Navy" was written in his usual lucid and attractive prose, and was published in the journals of the Society of Medical Officers of Health and of the Royal Navy Medical Service. He also wrote a reference book on industrial health which was officially approved and circulated to all medical officers. A new comprehensive handbook for medical and dental officers is being prepared, and he wrote the section on industrial medicine and some of the portions connected with hygiene and preventive medicine. He also gave lectures on industrial health to newly joined medical officers at the R.N. Medical School, Alverstoke. His contributions in hygiene, preventive medicine, and industrial medicine have been outstanding during recent years not only in the Navy but also in the Services Group of the Society of Medical Officers of Health and in conference at the Joint Services and Factory Committee on Occupational Health. He was also Naval secretary of the Epidemiology Section of the Royal Society of Medicine, as well as being on the committee of the United Services Section. He was awarded the Gilbert Blane medal in 1947 and the Parkes Memorial prize in 1955.

Geoffrey was a very conscientious, zealous, and likable medical officer. Modest and very unostentatious, he had great ability and much administrative acumen. His judgment was true, and he was always friendly and pleasant. His demise is a great loss to the Service which he loved and for which he did distinguished work. At home he took an interest in church affairs and was certainly a true practitioner of the Christian faith. Our deepest sympathy is tendered to his wife and son.

A friend writes: If it is old-fashioned to set oneself high ideals and to live by them, then Geoffrey Southwell-Sander was old-fashioned. The traditional loyalties were much more than mere traditions to him: he set his course by them. He found in the Senior Service a career which suited him down to the ground, for he enjoyed life in the Navy not only for its obvious advantages—he loved travel, for instance, and sport, and good fellowship—but also because it met his need for professional endeavour in the field of preventive medicine. Wherever he went the health and welfare of the men for whom he was responsible mattered intensely to him, and he obtained great satisfaction from his later work as a specialist in occupational health. With all this he had an enviable capacity for getting the best out of life. Knowledgeable and enthusiastic about history, art, literature, and music, he was the ideal travelling companion. His light-heartedness was infectious and his steadfastness in difficult times vastly encouraging. Devoted to his family, Geoffrey Southwell-Sander was a home-loving man, and it is indeed sad that he enjoyed for such a comparatively short time the new home near Dorking which he and his wife had made so elegantly their own. He died at the height of his career, leaving a widow and son whose friends will share their grief.

P. W. PHILIP, M.B., Ch.B.

Dr. Peter W. Philip, the last general-practitioner surgeon in Aberdeenshire, died at his home in Huntly on December 7 after a long illness. He was 58 years of age.

Peter William Philip was born on November 14, 1900, and studied medicine at Aberdeen University, where he graduated M.B., Ch.B. in 1924—the record post-war year of the Aberdeen Medical School. After graduation he had no hope of a house job in his teaching hospital in competition with ex-Service men who had but recently commanded men in battle, and he went as assistant to the late Dr. John O. Wilson at Huntly. There his work in the Huntly Cottage Hospital impressed the late Mr. F. K. Smith, visiting surgeon from Aberdeen Royal Infirmary, and he made Philip his house-surgeon a year after graduation and gave him special operative experience. Thereafter he returned to Huntly, this time as a partner, and for more than 30 years he served his people in the northern foothills of the Grampians. In that stormy rural area, 40 miles from Aberdeen, his undoubted skill as a surgeon saved many lives, but he was also a first-rate family doctor with a large practice.

His capacity for work and his zest for life gave him many activities outside his profession. He was a justice of the peace and an elder of the Scottish Kirk. A staunch conservative, he was vice-chairman of the West Aberdeenshire Conservative Association. In the medico-political field he was chairman of the Aberdeen and Kincardine Counties Division of the B.M.A. in 1951–2, a member of the local medical committee, and its representative on the Scottish Medical Services Subcommittee. He was a member of the local executive council since its inception. While he lifted trophies at bridge and bowls, his rarest pleasure was in fishing and shooting. As a raconteur he was in great demand at medical dinners, rotary clubs, and manifold societies. Unsparing of himself, he died in his prime, and our sympathy goes out to his widow, to his three daughters, one a doctor, and to his son.

D. G. G. writes: There was magic in the name of Peter Philip. Born a Buchan peasant—as pure a country stock as our Aberdeen-Angus cattle—lost as a student among so many ten-talented ex-Service men of the 1914–18 war, he yet blossomed forth to become one of the outstanding medical personalities of his generation in the North-east of Scotland. Stories of him were legion. He had become a legend in his own lifetime, and the legend will live for the rest of the century. His clothes the rough home-spun, his speech rich in his native Doric, his body strong to endure the long tramps through the snow-blocked roads, Philip of Huntly was loved by cottar and laird, both of whom he bullied impartially. Perhaps his best anecdote was of the patient who mistook a horse powder for a headache powder, and so often had he told it that it became a classic. But one he did not tell was of the case of post-partum haemorrhage in a lonely glen, when he took off nearly two pints of his own blood and transfused the patient. I remember when I was demobbed in the autumn of 1945 he came to stay a week-end with me to catch an Ythan salmon, and in his waders he had two bottles of Glenlivet, one for the ghillie and the other for his host.

The B.M.A. was dear to him, and he made a grand Division chairman. He relished his championship of the rural doctor and was a refreshing breeze among the cobwebs of St. Andrew's House in Edinburgh when he gave evidence before the jaded but delighted officials. Sir William Osler thought the lone figure in the gig, the rural doctor, the noblest figure in medicine: if Osler is waiting in the Elysian fields to welcome the country G.P.s, the front-line troops of the profession, then he will find in Peter Philip a common spark, and, who knows, there may be a Scottish burn there with deep salmon pools galore.

G. K. STRODE, M.D.

Dr. George K. Strode, formerly director of the International Health Division of the Rockefeller Foundation, died in the Memorial Hospital, Brattleboro, Vermont, on October 27. He was 72 years of age.

Sir ALLEN DALEY writes: The Old Guard of the Rockefeller Foundation of New York is dwindling rapidly as a result of death or retirement because of age. Within the past two years we have mourned the loss of Alan Gregg, the director of the Division of Medical Sciences, and of Pat O'Brien, a member of the same division. Now we learn of the death of Dr. George King Strode, the last director of the International Health Division. Just before he retired the Foundation had amalgamated the Divisions of Medical Sciences and International Health in a new division which it named the Division of Medicine and Public Health, with Strode as its first director.

Born in Pennsbury, Pennsylvania, George King Strode graduated in science from Haverford College in 1908 and in

medicine from the University of Pennsylvania in 1912. He was a Master of Public Health of Harvard. Soon after graduation he joined the staff of the state health department of Pennsylvania at Harrisburg. After seeing active service in France during the first world war he became, in 1920, a full-time officer of the Rockefeller Foundation. After his retirement in 1951 he lived in Whitingham, a remote spot in the State of Vermont. He worked for the foundation in Brazil until 1926 and from then until 1938 he was in charge of its medical and public health work in Europe, Africa, and the Near East, with headquarters in Paris. He was chairman of the Paris office from 1932 until he returned to New York in 1938. During the second world war he was a member of the American Red Cross Missions to Russia in 1941, Iceland in 1942, and North Africa in 1942–3. He had received decorations from many European countries, and was a Commander of the French Legion of Honour and an Honorary Fellow of the Society of Medical Officers of Health. A book on yellow fever which he edited was published in 1951.

Many Britishers retain happy memories of the warmth of the hospitality dispensed in their New York apartment by George Strode and his charming wife. He was a kindly and understanding man, beloved by all who had dealings with him. Wielding great power over the destinies of men and institutions of learning in many countries, he never let that go to his head or warp his judgment. George lived up to the motto of the Foundation, "The Welfare of Mankind throughout the World," and was always striving to achieve that aim somewhere. He guided the public-health work of the Rockefeller Foundation in the international field at a time when it was spending millions of dollars every year on its various and far-flung projects. The health and well-being of millions of people all over the world have benefited.

Medical Notes in Parliament

HOUSE OF LORDS

Injury from Nuclear Installations

The Nuclear Installations (Licensing and Insurance) Bill, which is intended to control in the interests of safety the building and operation of nuclear reactors and other fixed nuclear installations, completed its passage through the House of Lords on December 16. It authorizes, for this purpose, a system of licensing (excluding installations of the Atomic Energy Authority); and imposes on persons granted a licence to operate installations an absolute liability (similar to that of the A.E.A.) for all hurt to persons or damage to property caused by radiation, even though due to unavoidable accident. A licensee is obliged to take out cover, by insurance or other means, up to £5m. in respect of any one occurrence. The Bill as drafted also fixed the period within which claims for hurt or damage by radiation must be made at 10 years.

Objection was taken to this proposed time limit when the Bill was considered in committee, and Lord TAYLOR moved an amendment to delete it. Arguing that the Government were attempting to legislate for the unknown, he urged that the case against a 10-year limit was very strong. Diseases like leukaemia—bone sarcoma, aplastic anaemia, and aleukaemic leukaemia—were fatal, usually within a period of about five years. In many cases there was no known cause; but where there was a known cause the date of onset of a disease might be very much longer, and it was this latent period between the start of the cause and the development of the disease which was vitally important in connexion with the period in which a claim could be made. The principal hazard of a disaster in a nuclear plant was the liberation of radio-strontium, which could be picked up by the body and by a continuous process of radiation caused damage to the bone marrow, and ultimately death. The half-life of radio-strontium was 28 years, and the effect of radiation on the bone marrow appeared to be cumulative. This was a field of great technical difficulty, presenting medical research workers with the greatest problem, because no one knew exactly what the situation was. There was a useful analogous argument from radium and *x* rays; the first harmful effects of *x* rays were recorded in 1896, but it was not until 1914 that the first *x*-ray death in a radiologist occurred, from aplastic anaemia. The interval between the onset of the first changes as a result of *x*-irradiation and the development of malignant disease was anything between three and 27 years. On this experience the proper time limit, if there was to be one, should be some 30 years. The arbitrary choice of 10 years was unrealistic and not related to existing knowledge. Lord Taylor mentioned also the group of changes that could be caused by radio-caesium on the sexual cells, and the M.R.C. Report of 1956 and the U.N. Scientific Committee's Report this year which spoke of "a 30-year genetic dose."

The Minister of Power, Lord MILLS, expressed some sympathy with the purpose of the amendment, but objected that it would put an unlimited liability on the licensee and on insurance. The longer a claim was delayed the more difficult it would be for medical evidence to establish whether an injury was caused by exposure to radioactivity from the licensee's reactor at a particular time, or by something unconnected with it. A 10-year period was favoured by other member countries of the Organization for European Economic Co-operation, and was likely to be adopted for the purpose of any European convention on the insurance of nuclear risks. This argument was not accepted as convincing, and eventually Viscount HAILSHAM, Lord President of the Council, agreed that the matter should be given further consideration.

The subject came up again on the report stage on December 16, when Lord MILLS brought in a Government amendment to provide a time limit of 30 years. The Opposition still found any time limit unacceptable, on the ground that they were dealing with a type of injury which even the most eminent scientists did not understand. They carried their objections to a division, in which a proposal by Lord SILKIN to remove the time limit altogether was defeated by 69 votes to 37. The Government amendment was then agreed to and the Bill given its third reading.

Adequacy of Mental Research Programmes

Lord STONHAM asked on December 11 if the Government were aware that only 2% of the Medical Research Council's budget was spent on research into the causes of mental illness, and whether, having regard to the statement in the Report of the Ministry of Health for the year 1957 that "psychiatrists are still a long way from a scientific understanding of most of the major forms of mental illness," they would take steps to increase facilities for such research.

The Lord President of the Council, Viscount HAILSHAM: "No, my Lords." The Medical Research Council's expenditure on research into the causes of mental illness had been steadily rising during the past few years, and in the present financial year would amount to some £130,000. This was over 4%, and not 2%, of the Council's annual budget. Arrangements had recently been made by the Council to undertake a full-scale review of research in this field with a view to considering its future development. In addition, a number of voluntary organizations and philanthropic trusts, such as the Mental Health Research Fund, the Nuffield Foundation, the Wellcome Trust, and the Ford Foundation, made important contributions to psychiatric research. The Mental Health Research Fund, for example, spent about £36,000 during the financial year 1957–8, and their total expenditure since 1954 was estimated at £86,000. During the past five years the Nuffield Foundation had also spent a substantial sum on subjects relevant to mental disorder. The Leverhulme Trust and the Ford Foundation had made large block grants to the Mental Health Research

Fund; and the Wellcome Trust had made direct contributions to work in this field. As "observational" research might be an integral part of clinical practice, the work of those in psychiatric practice in teaching and mental hospitals should be included in the total sum of the nation's research, but this could not be measured in exact financial terms nor described as a specific research programme. Certain London teaching hospitals, for example, had active neuropsychiatric units to which research fellows, supported by endowment funds, were appointed by the hospitals themselves. Research of this kind was also supported at many other hospitals through regional hospital boards. Expenditure within the Health Service in this way was estimated at £25,000 for 1957. University psychiatric departments also made individual contributions to research in this subject.

QUESTIONS IN THE COMMONS

Hospital Building Programme 1960–1

Sir KEITH JOSEPH (Leeds, North-east, Con.) asked the Minister of Health on December 17 whether he was now in a position to make a further statement about the Government's hospital building programme. Mr. D. WALKER-SMITH: "Yes. It is proposed, subject to the voting by Parliament of the necessary funds, that £25½m. shall be spent on capital development in the hospital service in England and Wales in 1960–1, compared with £22m. already announced for next year, 1959–60." Hospital boards, said the Minister, were being informed of their individual allocations within this total for the modernization of mental hospitals, the replacement of obsolete plant, and ordinary capital expenditure. £10m. would be set aside for the programme of major projects which were financed centrally. This programme would be further expanded, and he was that day inviting boards to bring to completion the planning of a number of additional major projects. He hoped that they would try to complete the planning by 1960–1.

Mr. Walker-Smith went on to say that he had already authorized the arranging of an architectural competition which was in hand for the planning of the new Cardiff teaching hospitals; and he was also considering what dental hospital projects should be undertaken to increase the output of the dental schools.

The major new building projects now selected included the first phases of new general hospitals for north Tees-side and at Northwick Park for the Wembley–Harrow area; a further stage of the new Sheffield teaching hospital of which the out-patient department was now being built; the start of the reconstruction of Queen Mary's Hospital, Sidcup; a blood transfusion centre at Liverpool; and later stages of some new hospitals already in the programme. There would be new radiotherapy departments at Newcastle, Sheffield, and Birmingham.

In the sphere of large-scale extensions a large extension of the High Wycombe Memorial Hospital was proposed and a number of other hospitals were to be improved or developed. They were Crewe Memorial Hospital; the Mayday Hospital, Croydon; Queen Mary's, Stratford; the Royal Gwent Hospital, Newport; Southampton General Hospital; and St. Stephen's Hospital, Fulham Road. There was a new maternity wing at Billinge Hospital, Wigan, and a new maternity unit was included in proposals for expanding the Yeovil and District Hospital. Further development would be undertaken at the Good Hope Hospital, Sutton Coldfield, and at the Coventry and Warwick Hospital. He was also increasing the allocations made last year in order to allow development to take place at both Ilford and Barking, and to permit as the first phase of hospital development in Hull the improvement of the Western General Hospital. He was also asking for plans to be prepared for certain hospital development in Bradford, and details of this would be worked out with the Leeds Regional Hospital Board.

In the mental health field the Minister proposed to provide additional beds at the mental deficiency hospitals at Greaves Hall, Southport, Cranage Hall, Holmes Chapel, and Oakwood Park, Conway; extensions to Borocourt (near Reading) and Little Plumstead (near Norwich) Mental Deficiency Hospitals; improvements at Fulbourne Mental Hospital, near Cambridge; and new long-stay annexes at Lynfield Mount Mental Hospital, Bradford. A psychiatric block was also to be provided at the new Welwyn Hospital which was now being built.

Hallucinogenic Drugs

Dr. DONALD JOHNSON (Carlisle, Con.) asked the Home Secretary if he was aware of the dangerous hallucogenic properties of such new drugs as mescalin and lysergic acid diethylamide, and when he proposed to bring them under the Dangerous Drugs Acts. Mr. BUTLER stated on December 11 that he was informed there was no evidence that these drugs were addiction-producing. It would not therefore be appropriate to control them under the Dangerous Drugs Act, 1951.

Legal Actions in the Health Service

Dr. JOHNSON asked the Minister of Health if he would state the number of legal actions in which the Health Service, or any of its employees, had been defendant in each year since the inception of the Service. What had been the total cost to the Exchequer in settling such actions, including those settled out of court? Mr. R. THOMPSON, Parliamentary Secretary, stated on December 12 that the only statistics centrally available were the total amounts paid in compensation of all kinds by hospital authorities and executive councils in England and Wales, whether or not legal action was involved. These were as follows:

Period ended March 31	£
1949	7,560
1950	23,636
1951	38,556
1952	106,574
1953	152,590
1954	159,047
1955	91,535
1956	110,321
1957	116,136
1958	100,826

Nuclear Information Withheld from M.O.H.

Mr. W. COLDRICK (Bristol, North-east, Lab.) asked the Minister of Housing and Local Government why he had declined to supply the M.O.H. for Bristol with the whereabouts of the sources of various radioactive materials in the city. Mr. J. R. BEVINS, the Parliamentary Secretary, told him on December 9 that in supplying radioisotopes the Atomic Energy Authority acted as a commercial concern, and it was not normal practice to make known the full details of such transactions. The Department followed up deliveries and was able to ensure that any requisite statutory consent for disposal of waste was obtained from the appropriate authorities. The Minister had assured the M.O.H. for Bristol that there was no danger to public health from disposals of radioactive waste in his area.

Parking Meters in St. Marylebone

Sir WAVELL WAKEFIELD (St. Marylebone, Con.) asked the Minister of Transport and Civil Aviation what progress he had made in connexion with approving the establishment of a parking scheme for St. Marylebone. Mr. H. WATKINSON told him on December 10 that he had fully considered the St. Marylebone Borough Council parking scheme in the light of the objections made to it, the report of Sir Reginald Sharpe, who conducted a public inquiry, the report of the London and Home Counties Traffic Advisory Committee, and the results of the experiment in North-west Mayfair. He had decided to approve the scheme with some modifications: when these had been settled he would make the necessary Order and Regulations.

Vital Statistics

Accidental Deaths Increase

In the third quarter in England and Wales accidental deaths numbered 3,550, or 146 more than in the third quarter last year, according to the Registrar-General's return for the third quarter. A notable increase was deaths from coal-gas poisoning—from 68 last year to 114 this year. The total of home accidents in the third quarter this year, 1,234, was 44 lower than last. The accidental deaths in the quarter were as follows:

	Age		
	0–14	15–64	65 and Over
Home accidents	111	223	900
Transport ,, ...	217	978	313
Other ,, ...	160	490	158

They show that twice as many children were killed on the road as in the home, and three times as many old people in the home as on the road.

Week Ending December 6

The largest fluctuations in the notifications of infectious diseases in England and Wales during the week ending December 6 were increases of 1,472 for measles, from 6,910 to 8,382, 89 for acute pneumonia, from 407 to 496, 53 for scarlet fever, from 1,164 to 1,217, and 25 for whooping-cough, from 724 to 749; the largest decreases were 78 for dysentery, from 1,098 to 1,020, and 58 for food-poisoning, from 236 to 178.

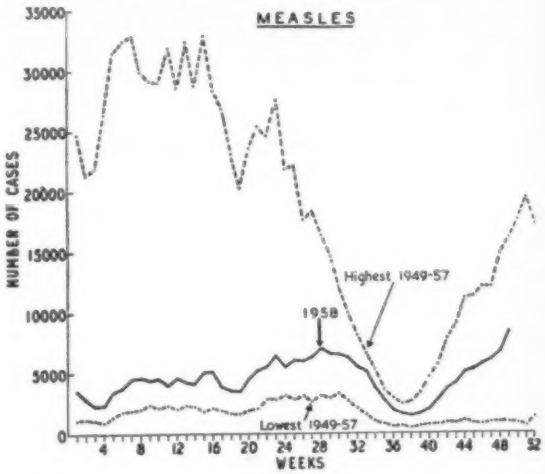
The largest rises in the incidence of measles were 188 in Lancashire, from 739 to 927 (Liverpool C.B. 136, Manchester C.B. 116), 163 in London, from 398 to 561 (Wandsworth 109, Hammersmith 84, Paddington 78), 161 in Staffordshire, from 209 to 370 (Newcastle-under-Lyme M.B. 75), 114 in Yorkshire West Riding, from 837 to 951 (York C.B. 188, Halifax C.B. 104). The largest rise in the number of notifications of scarlet fever was 34 in Essex, from 72 to 106. Only small changes occurred in the local trends of whooping-cough. 4 cases of diphtheria were notified, being 3 fewer than in the preceding week; no administrative area had more than 1 case.

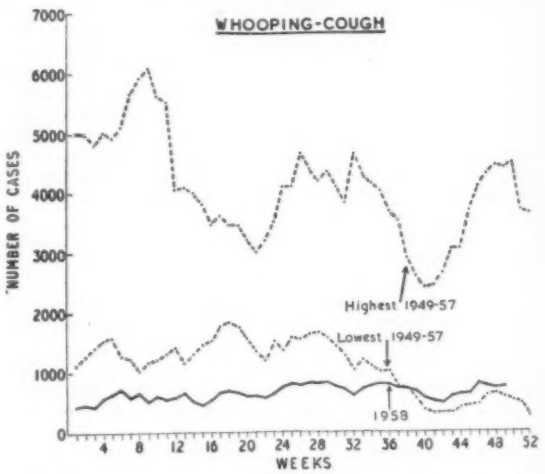
The notifications of acute poliomyelitis numbered 53, and these were 9 fewer for paralytic and 7 fewer for non-paralytic cases than in the preceding week. The largest returns were Lancashire 9 (Manchester C.B. 4), London 7 (Islington 2), Yorkshire West Riding 7 (Huddersfield C.B. 2), Hampshire 5 (Southampton C.B. 4).

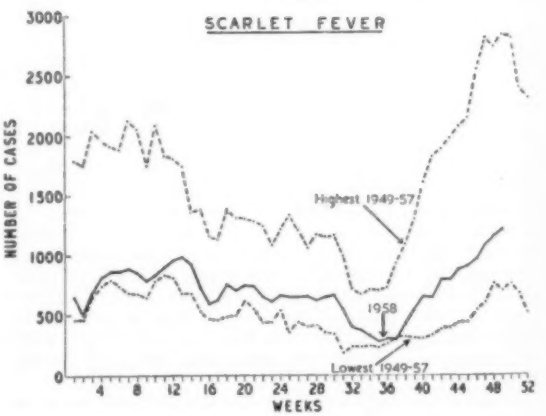
The largest falls in the incidence of dysentery were 56 in Yorkshire West Riding and 45 in Warwickshire. The chief centres of infection during the week were Yorkshire West Riding 120 (Leeds C.B. 73, Huddersfield C.B. 12), Glamorganshire 127 (Cardiff C.B. 63, Llantrisant and Llantwit Fardre R.D. 30, Rhondda M.B. 26), Lancashire 101 (Eccles M.B. 15, Liverpool C.B. 13, Nelson M.B. 13), Middlesex 95 (Hendon M.B. 79), London 88 (Battersea 19, Wandsworth 12, Kensington 10), Warwickshire 71 (Coventry C.B. 60, Birmingham C.B. 10), Essex 55 (Rochford R.D. 19, East Ham C.B. 16), Kent 40 (Maidstone R.D. 13, Royal Tunbridge Wells M.B. 11), Hertfordshire 39 (Welwyn Garden City U.D. 36), Northumberland 34 (Ashington U.D. 14, Newbiggin-by-the-Sea U.D. 12), Surrey 27 (Coulsdon and Purley U.D. 19), Yorkshire East Riding 25 (Kingston upon Hull C.B. 20), Durham 23, Hampshire 21 (Southampton C.B. 15), Bedfordshire 21 (Ampthill R.D. 21), Staffordshire 21.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus - - - - - -, the figures for 1958 thus ———. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **December 6** (No. 49) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria	4	1	5	0	2	1	0	1	0	5
Dysentery	1,020	88	212	15	8	576	135	186	9	1
Encephalitis, acute	2	0		0		1	0		0	
Enteric fever:										
Typhoid	1	0	0	0		3	1	0	0	1
Paratyphoid	2	0	2(B)	0	2(B)	6	0	0	0	
Food-poisoning	178	24	16	2		146	18	23	0	
Infective enteritis or diarrhoea under 2 years				13	38				7	17
Measles*	8,382	561	139	46	550	2,214	44	36	30	24
Meningococcal infection	28	1	13	0	1	29	1	9	3	1
Ophthalmia neonatorum	27	7	2	0		14	2	4	0	
Pneumonia†	496	35	250	9	2	649	38	313	5	38
Poliomyelitis, acute:										
Paralytic	41	7	3	0	4	61	1	3	4	1
Non-paralytic	12	0				20	0			
Puerperal fever§	206	31	5	2		188	36	7	1	
Scarlet fever	1,217	94	104	20	30	723	50	59	13	16
Tuberculosis:										
Respiratory	489	54	115	14		510	53	97	15	
Non-respiratory	50	0	12	2		72	5	8	2	
Whooping-cough	749	14	81	85	67	575	24	64	4	21

DEATHS	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria	0	0	0	0	0		0	0	0	0
Dysentery	0	0		1			0		0	
Encephalitis, acute		0			0		1			0
Enteric fever	0	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	8	0	0	0	0		0	0	0	1
Influenza	23	2	1	0	0		14	4	0	14
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	613	47	19	22	7		71	33	15	11
Poliomyelitis, acute	4	1		0	0		0		0	0
Scarlet fever		0		0	0		0	0	0	0
Tuberculosis:										
Respiratory	115	6	9	0	3		8	7	1	5
Non-respiratory		0	0	0	0		2	1	0	0
Whooping-cough	0	0	0	1	0		0	0	0	0
Deaths 0–1 year	313	29	23	10	13		22	34	5	11
Deaths (excluding stillbirths)	10,926	876	700	147	151		1090	638	135	186
LIVE BIRTHS	13,696	1136	1003	235	287		1045	955	210	328
STILLBIRTHS	325	30	35				26	20		

No comparable figures available.

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

New Hospital Board.—From April 1, 1959, the Wessex Regional Hospital Area is to be formed from what is now the western portion of the South-west Metropolitan Regional Hospital Area. A regional hospital board will be constituted for it (S.I. 1958, No. 2093).

Association for the Study of Medical Education.—The Rockefeller Foundation has made a grant of £10,000 to the Royal College of Physicians for use towards the general expenses of the Association for the Study of Medical Education during the first five years of its development.

Chemists' Federation.—The Federation has announced its dissolution as from December 31. This follows the recent judgment by the Restrictive Practices Court (*Journal*, November 15, p. 1236). The Federation comments in a statement as follows: "As a result of this judgment it remained open to the Registrar under section 20 of the Act to apply to the Court for an injunction restraining members of the Federation from giving effect to, or enforcing, or purporting to enforce the agreement. The Chemists' Federation council, after taking legal opinion, decided that the dissolution of the Federation was necessary in order to protect the rights of the individual member."

Prescribed Industrial Diseases.—A right of appeal from medical boards' decisions on whether or not a person claiming benefit under the industrial injuries scheme is suffering from one of certain prescribed industrial diseases is provided by new regulations made by the Minister of Pensions and National Insurance (S.I. 1958, No. 2112, H.M.S.O., price 3d.). These regulations will apply to decisions given by medical boards on or after January 5. Appeals will be decided by the same tribunals as already consider appeals against boards' assessments of extent of disablement.

Chief Medical Adviser, Nigeria.—Dr. C. M. NORMAN-WILLIAMS will succeed Sir SAMUEL MANUWA as Chief Medical Adviser to the Federal Government of Nigeria, on the latter's retirement on January 2.

Mr. B. W. Rycroft has been elected honorary member of the Ophthalmological Societies of New Zealand, Australia, and South Africa.

COMING EVENTS

"Alcoholism and Drug Addiction."—Week-end course (£3 15s.) arranged by the Institute for the Study and Treatment of Delinquency, January 2–4, at Avoncroft College, Bromsgrove. Details from I.S.T.D., 8, Bourdon Street, Davies Street, London, W.1. (MAYfair 3472.)

London Medical Orchestral Society.—Informal concert including works by Rossini, Beethoven, and Haydn, January 17, 7.30 p.m., at Quintin School, Marlborough Hill, London, N.W.8. Admission free.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Friday, January 2

ROYAL MEDICO-CHIRURGICAL SOCIETY OF GLASGOW.—At Royal Faculty of Physicians and Surgeons of Glasgow, 8.30 p.m., discussion: Management of Incurable Illness. Panel, Dr. W. F. Anderson, Dr. A. McCrone, Mr. J. L. Orr, and Miss A. Keen.

Saturday, January 3

MIDLAND THORACIC SOCIETY.—At Birmingham Medical Institute, 3 p.m., short papers by Dr. J. Aspin, Mr. E. G. Dolton, and Dr. J. Leahy.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Lindan.—On December 12, 1958, at Cleveland, Ohio, U.S.A., to Dr. Rosemary Lindan (formerly Jackson), and Olgierd Lindan, M.D., Ph.D., a sister for Nicholas and Christina—Camilla Elspeth.

Twidle.—On December 10, 1958, at Sheffield, Yorks, to Ruth Carol (formerly Wiltsie), wife of Surgeon Lieutenant Robert S. H. Twidle, R.N., a son.

DEATHS

Wardale.—On December 7, 1958, at his home, near Haydon Bridge, Northumberland, John Dobson Wardale, M.B., B.S., aged 90.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Sequestrenized Blood for Transfusion

Q.—*Is sequestrenized blood better for routine transfusions than citrated blood, and how is it prepared ?*

A.—Sequestrene (Na_2, ethylene diamine tetracetic acid) is accepted as the anticoagulant of choice in the preparation of whole blood or platelet concentrates for transfusion.[1] For this purpose the anticoagulant should be contained either in a siliconed bottle or in a plastic bag. The platelet transfusion may be given either as fresh whole blood, platelet-rich plasma, or as a platelet concentrate in its own plasma or saline. If transfused within a few hours after collection good results are to be expected. Where there is severe thrombocytopenia the platelets from 4 pints (2.3 l.) of whole blood should be given either as whole blood or as a concentrate. After such a transfusion it is not uncommon for there to be an improvement in the clinical state of the patient without any detectable rise in the number of circulating platelets.

Sequestrene solutions can be sterilized by autoclaving without loss of activity. The amount of sequestrene necessary to inhibit the coagulation of 97 ml. of blood is 3 ml. of a 4.5% w/v isotonic solution.[2] Alternatively 10 ml. of a 1% solution of sequestrene in saline may be used for 90 ml. of blood.[3] With small volumes of anticoagulant efficient mixing of the blood and anticoagulant at the time of collection is important. The ability of platelets to improve haemostatic function on transfusion is impaired after 12 hours, and after 24 hours' storage the platelets would appear to be quite inactive in this respect.

Sequestrene does not appear to have any advantage over citrate apart from its use in platelet transfusions. When mixed with dextrose it preserves red cells as well as acid citrate dextrose.[2] While no toxic effects have been recorded in humans, it can be presumed, on the basis of rabbit experiments,[4] that 7 g. administered to a 70-kg. human might produce tetany. This would represent approximately a 10-pint (5.7-l.) transfusion of blood collected in 4.5% sequestrene. If citrate intoxication is considered to be a danger, such as in exchange transfusion, heparin remains the anticoagulant of choice.

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1 Stefanini, M., *Arch. intern. Med.*, 1955, **95**, 543.
2 Sprague, C. C., Harrington, W. J., Lange, R. D., and Shapleigh, J. B., *J. Amer. med. Ass.*, 1952, **150**, 1193.
3 Mollinson, P. L., *Blood Transfusions in Clinical Medicine*, 1956. Blackwell Scientific Publications, Oxford.
4 Proescher, F., *Proc. Soc. exp. Biol., N.Y.*, 1951, **76**, 619.

Internal Medicine

Q.—*What is the significance of the term "internal" as applied to medicine ?*

A.—The word "internal" applied to the province of the physician in the vast field of medicine seems to have been introduced by the German schools early last century, when the term *Innere Medizin* was coined. It is not, perhaps, the most suitable adjective, but it seems to be useful and essential as a successor to the earlier term "practice of physic," which is still used in certain universities. The wide applicability of the word "medicine" is unfortunate. It may be applied to (1) a drug or remedy, (2) the entire field of the prevention and cure of disease, and (3) medicine as opposed to surgery. For centuries it was actually opposed, and the surgeon was a mere craftsman. When surgery, and also obstetrics, became a part of medicine or medical knowledge, and when there arose, besides these two, a large number of specialties which also belonged to "medicine," the need to distinguish all these facets of medical knowledge became obvious, and there appeared forensic medicine, social medicine, preventive medicine—and internal medicine. Perhaps "internal" signified the diseases which were medical and incurable to distinguish them from diseases surgical and curable, as some wag once said. Internal medicine is a term now in general use, whatever the reason of the choice of adjective.

Mumps Orchitis

Q.—*What is the latest form of treatment—prophylactic and therapeutic—of mumps orchitis ?*

A.—Antibiotics are of no value in the treatment of mumps. If orchitis develops cortisone may be tried; 300 mg. should be given by mouth as the first dose, followed by 100 mg. every six to eight hours for two to four days. Sometimes the effect is dramatic, symptoms subsiding within 24 hours. Orchitis has, however, developed in the unaffected testicle during cortisone treatment so that there seems to be no grounds for the prophylactic use of the drug.

Control of Haemophilia

Q.—*What specific therapy is of value in the prevention and treatment of bleeding episodes in haemophilia ? Is any other drug therapy of value ?*

A.—Haemophilia is caused by a congenital deficiency in the blood of a factor (antihaemophilic globulin) required for normal coagulation. The only treatment which can prevent or cure bleeding is the replacement of this substance in the patient's blood. The substance may be supplied by the transfusion of whole fresh blood or fresh plasma. To be effective it is necessary to use large amounts of blood or plasma. For an adult patient haemostatic levels of antihaemophilic globulin are not achieved with less than a litre of fresh plasma, and most of the activity disappears from the patient's blood in 24 hours. For this reason it is most desirable to have a concentrated form of antihaemophilic globulin. Concentrated material from human blood is now made in small amounts by the Lister Institute in London, and has proved useful for dental extractions and relatively minor procedures. Antihaemophilic globulin made from animal blood has been made and used successfully for volunteers and for dangerously ill patients at Oxford,[1–4] and is now available commercially, but, like the human material, only to haemophilia centres.

It seems to be the general experience of medical workers that the egg-white preparation mentioned in the question has no effect on the coagulation defect in haemophilia.

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